Global Bio Conference

June 27(Mon) ~ July 1(Fri), 2016
InterContinental Seoul Coex

• Host | Ministry of Food and Drug Safety • Organizer | KoBIA 한국바이오의약품협회

Federal Institute for Vaccines and Biomedicines

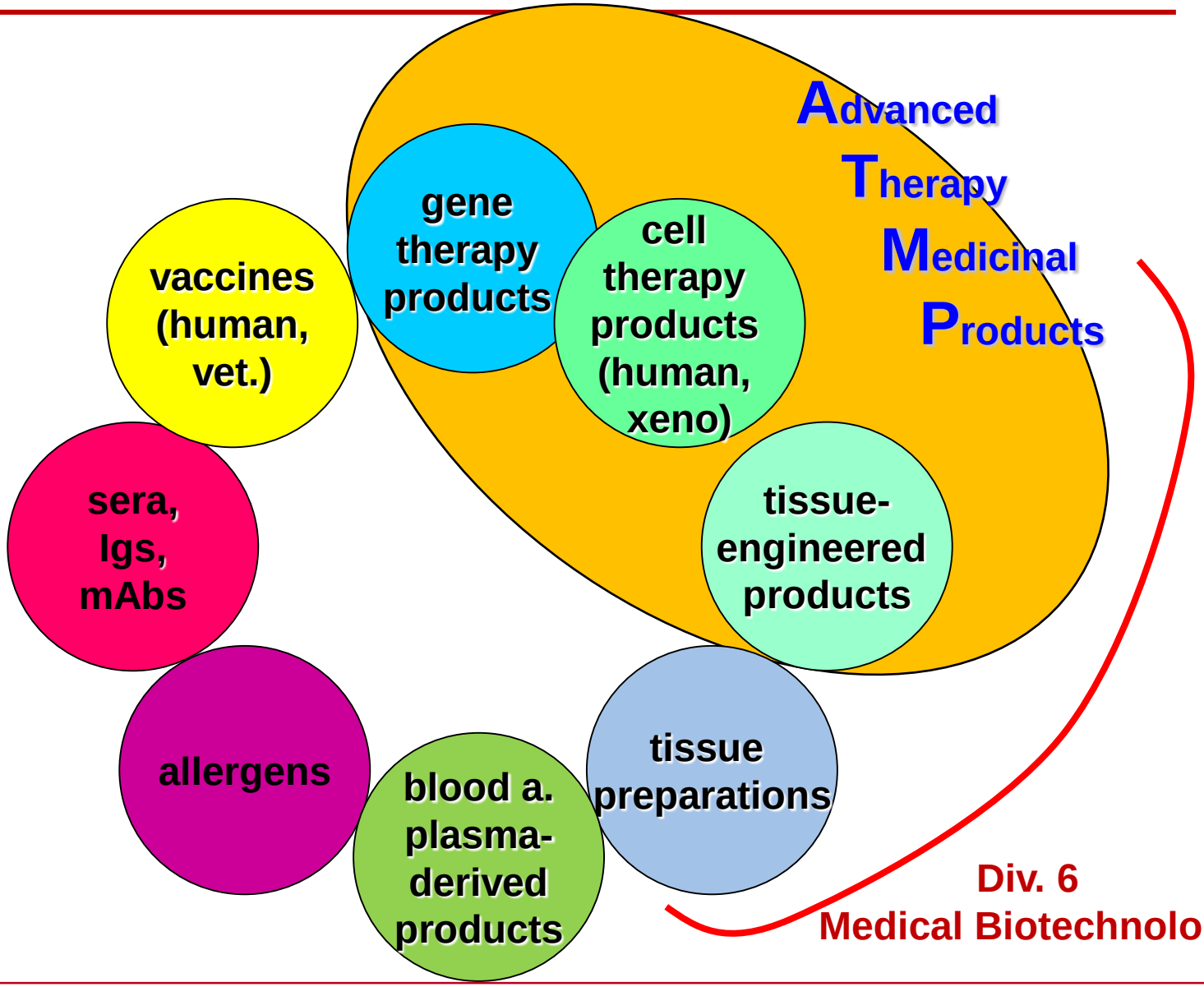
Paul-Ehrlich-Institut

www.pei.de

Regulatory aspects and challenges of gene therapy medicinal products in Europe and Germany

Matthias Schweizer
Division of Medical Biotechnology
Global Bio Conference, Seoul
June 28th, 2016

Medicinal products at the Paul-Ehrlich-Institut



Regulatory Activities of PEI on ATMP

National

- Approval of Clinical Trials
- Approval of Hospital Exemptions
- National Scientific Advice
- involved in Manufacturing Authorization *(responsible: german federal states)*
- Inspections (specific, product-related questions**)**

EU *(via EMA / CAT)*

- Rapp/Co-Rapp for MAAs; Draft opinion to CHMP
- Variations
- EMA scientific advice *(via SAWP)*
- Guideline development
- Classification *(Is a product an ATMP ?)*
- Certification *(Q/N-C review, for ATMP only, for SME only)*
- PIP of ATMP *(via PDCO)*
- ITF Briefing Meetings

EDQM

- European Pharmacopoeia
- OMCL

Agenda

1) ATMP regulation in EU

Activities of the CAT

Classification of gene therapy medicinal products

Licensed ATMPs in Europe

European scientific guidelines on GTMP

2) Clinical gene therapy trials in Germany

3) Regulatory activities to foster development of ATMPs in Europe

Legal Basis of ATMP Regulation

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

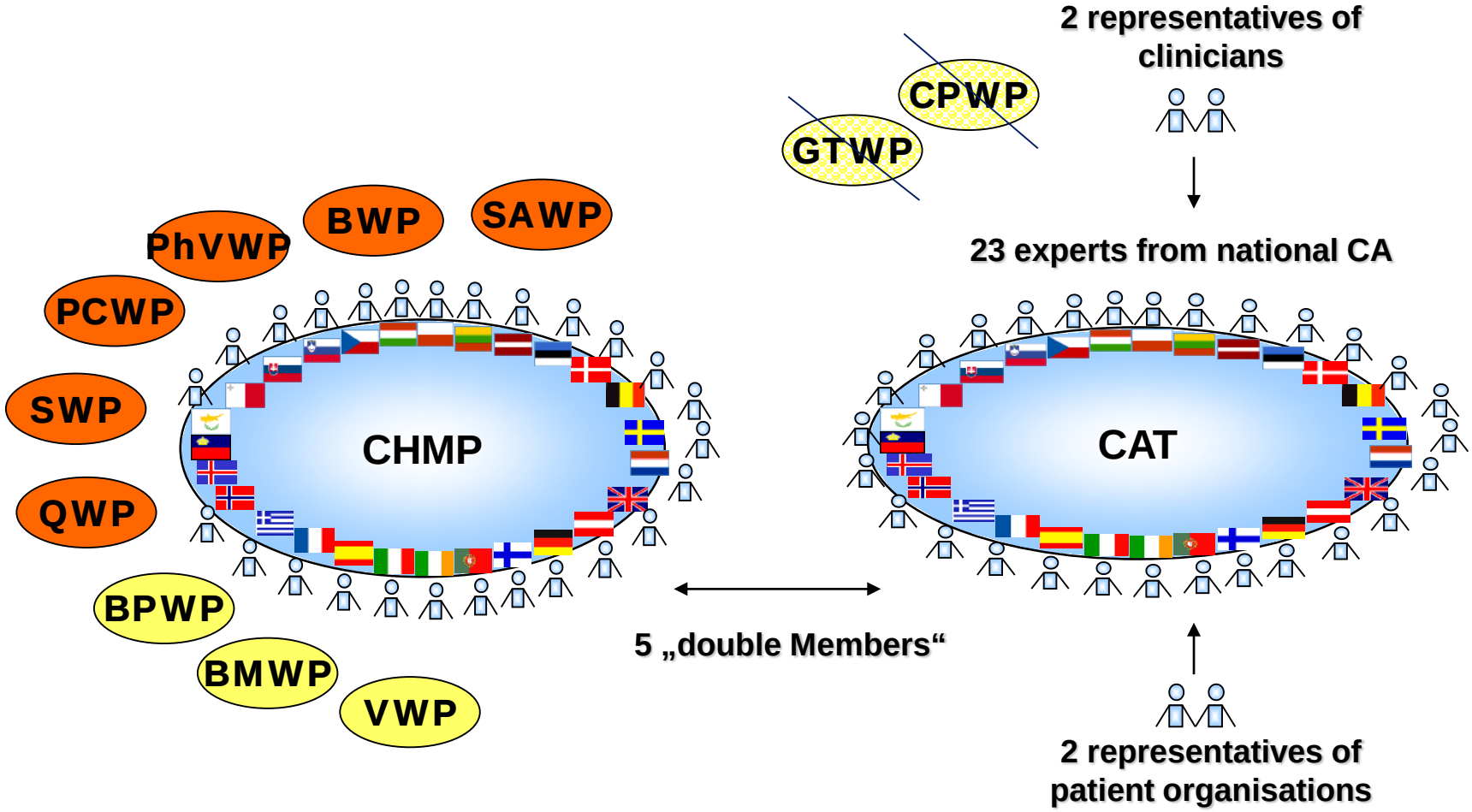
COMMISSION DIRECTIVE 2009/120/EC

of 14 September 2009

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

(Text with EEA relevance)

Committee for Advanced Therapies (CAT)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Tasks of the CAT

- **Classification procedure**

  Is a product an ATMP ?

  → Scientific recommendation from CAT

- **Certification procedure**

  Q/N-C review (for ATMP only, for SME only)

- **Scientific assistance**

  - Development of guidelines on ATMP
  - Scientific Advice of ATMP (SAWP responsibility)
  - PIP of ATMP (PDCO responsibility)
  - ITF Briefing Meetings

- **Draft opinion** to CHMP on marketing authorisation of ATMPs

Definition of Gene Therapy Medicinal Products in EU

Experience with CAT classification procedures

COMMISSION DIRECTIVE 2009/120/EC

of 14 September 2009

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

2.1. **Gene therapy medicinal product**

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

Definition of Gene Therapy Medicinal Products in EU

Experience with CAT classification procedures

Clincal effect of product does not relate to recombinant nucleic acid : *no GTMP*

Examples: iPS cells

suicide gene as safety measure (Zalmoxis)

Vectored vaccines against infectious diseases: *no GTMP*

Examples: MVA- or Adenovirus-based vaccines against HIV-1

However: vector vaccine directed against HPV epitopes:

for vaccination against virus infection: no GTMP

*for vaccination against cervical carcinoma: **GTMP !!***

Dendritic cells transfected with mRNA:

***no** GTMP (if mRNA is completely degraded at the time of application)*

Activities of CAT 2009-2016 (May)

	2009	2010	2011	2012	2013	2014	2015	2016	total
MAA´s*	3	1	2	3	2	2	1		**15**
Classification	22	19	12	22	20	28	61	36	**220**
Certification	1	0	0	1	3	1	1	1	**8**
SA	25	30	36	31	36	48	63	32	**301**
PIP	4	7	6	9	7	7	3	2	**45**

*** 15 MAA´s:**

Positive opinion: **7 (3 GTMP)**

Withdrawals: **4 (4 GTMP)**

Ongoing: **4 (no GTMP)**

ATMPs authorized in EU (1)

Name	Active substance	Therapeutic area	Year of authorization
ChondroCelect	Autologous cartilage cells expanded *ex vivo*	Cartilage Diseases	2009
Glybera (Exc. circumst.)	AAV1 vector transferring LPL gene	Hyperlipoproteinemia Type 1	2012
Maci	Autologous cultured chondrocytes	Fractures, Cartilage Diseases	2013 *(suspended)*
Provenge	CD54+ cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor	Prostatic neoplasms	2013 *(2015: withdrawn)*
Holoclar	*ex vivo* expanded autologous human corneal epithelial cells containing stem cells	Limbal stem-cell deficiency	2014

ATMPs authorized in EU (2)

Name	Active substance	Therapeutic area	Year of authorization
Imlygic	Oncolytic replication-competent virus derived from attenuated herpes simplex virus 1 transferring GM-CSF gene	Inoperable melanoma that has spread to other parts of the body	2015
Strimvelis	autologous CD34+ cells transduced to express ADA	ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency)	2016

Reasons for non-approval of gene therapy medicinal products in Europe:

No positive benefit-risk-ratio demonstrated !

Negative CHMP decisions were **not** due to gene therapy-specific safety concerns, such as

- Possible risk for the environment (e.g. shedding of infectious virus)
- Insertional mutagenesis (induction of cancer)
- Germ line integration

Objections regarding Quality and Safety seem to be resolvable/acceptable.

Efficacy remains to be the highest hurdle to overcome.

Possible reasons:

- “Real” lack of therapeutic efficacy
- Methodological problems in measuring efficacy
- Orphan disease (low patient numbers)

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EMA Scientific Guidelines on GTMPs

General

EMA/CAT/80183/2014 (Draft)
Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products

(substitutes previous guideline)

EMA/CHMP/GTWP/212377/2008
Questions and Answers on Gene Therapy
(e.g. on Quality: comparability / full sequencing / residual host cell DNA / resistance gene / potency test)

EMA Scientific Guidelines on GTMPs

Product specific

CPMP/BWP/2458/03
Guideline on Development and Manufacture of Lentiviral Vectors

CHMP/ICH/607698/2008 **Oncolytic Viruses**

CHMP/GTWP/587488/2007
Reflection Paper on Quality, Non-Clinical and Clinical Issues related to the Development of Recombinant Adeno-Associated Viral Vectors

CAT/GTWP/671639/2008
Guideline on quality, preclinical and clinical aspects of medicinal products containing Genetically Modified Cells

EMA Scientific Guidelines on GTMPs

Specific issues of GTMPs

EMEA/273974/05
Non-Clinical testing for Inadvertent Germline Transmission of Gene Transfer Vectors

EMA/CAT190186/2012
Reflection paper on management of clinical risks deriving from insertional mutagenesis

CHMP/GTWP/125491/06
Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products

CHMP/ICH/449035/09
ICH Considerations: General Principles to Address Virus and Vector Shedding

EMA Scientific Guidelines on GTMPs

Specific issues of GTMPs

EMEA/CHMP/GTWP/125459/06
Non-Clinical Studies required before first Clinical Use of Gene Therapy Medicinal Products

EMEA/GTWP/60436/07
Follow up of patients administered with gene therapy medicinal products

5.14. Gene Transfer Medicinal Products for Human Use

- Recombinant vectors
- Genetically modified cells
- Plasmid vectors
- Bacterial cells used for the manufacture of Plasmid vectors
- Adenovirus vectors
- Poxvirus vectors
- Retroviridae-derived vectors
- Adeno-associated-virus vectors

IMP has to be manufactured according to GMP!

COMMISSION DIRECTIVE 2009/120/EC

of 14 September 2009

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products

(Text with EEA relevance)

3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells.

The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

Also vectors used to modify cells ex vivo have to be manufactured according to GMP!

Regulatory activities to foster development of MPs in Europe

Draft:

“GOOD MANUFACTURING PRACTICE FOR

ADVANCED THERAPY MEDICINAL PRODUCTS”

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Institutions involved in CTA of ATMPs in Germany

Paul-Ehrlich-Institut *(Institution of the German Ministery of Health)*

(Approval of clinical trial)

Federal State Authorities

(Manufacturing or import authorization, inspections, Gene law)

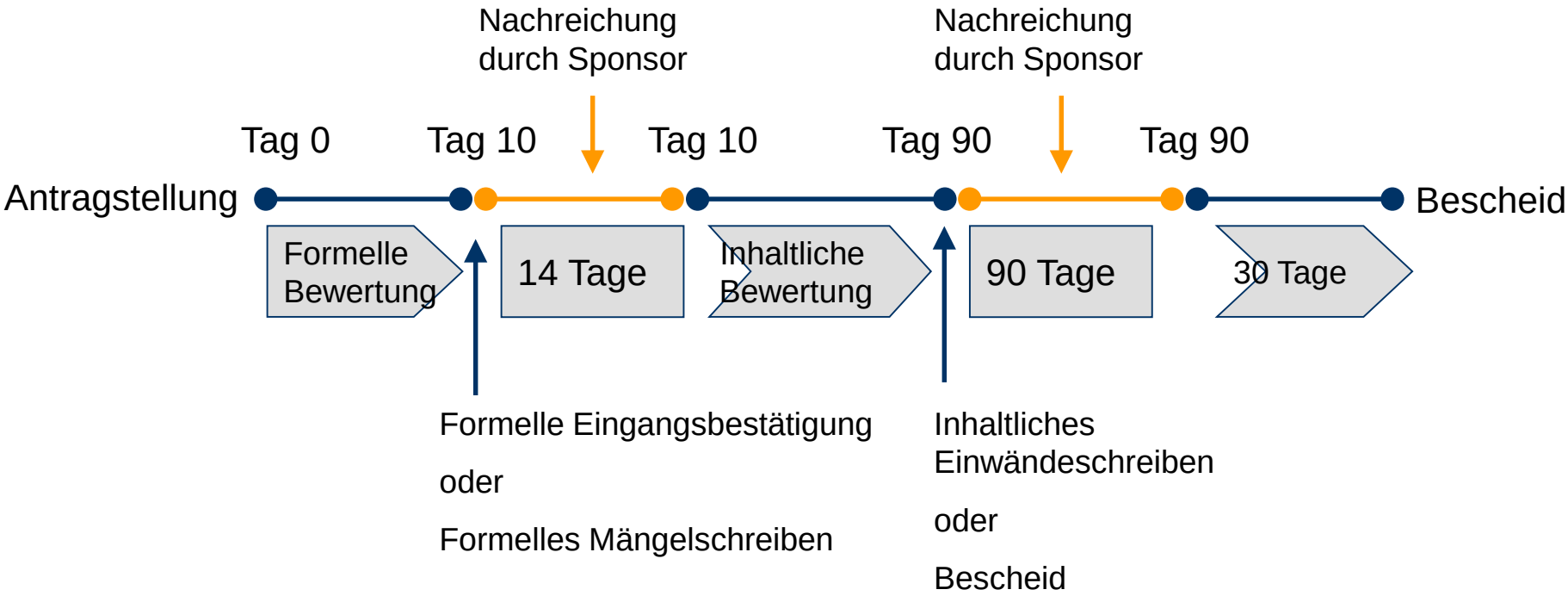
Local Ethics Committee

(Ethics committee vote)

Federal Office of Consumer Protection and Food Safety
(Institution of German Federal Ministry of Food and Agriculture)

contacted bei PEI concerning Environmental Risks

Timelines of clinical trial approval



Documentation required for Clinical trial application

1) Quality (safe and consistent manufacturing)

2) Preclinical (Safety, Efficacy)

3) Clinical (study plan)

4) ERA (mandatory for products containing GMOs)

(in addition, a number of formal information required)

(Documentation form on the basis of CTD for licensing)

Clinical GT Trial Applications in Germany (PEI)

August 2005 – May 2016*

clinical use	number (80 trials)
cancer	58
cardio-vascular	8
stroke	2
diabetes	1
HIV infection	1
neuronal	1
monogenic inherited disorder	9
hemophilia B factor IX	1
CGD gp91phox	2
Eye disease	5
β-Thalassemia	1

***1994-2004: 64 clinical GT trials have been "approved" in Germany before Clinical Trial Directive 2001/20/EC came in force**

Clinical GT Trial Applications in Germany (PEI)

August 2005 – May 2016*

Ex vivo (29)	**AAV**	**2**
	Onco-retroviral	**15**
cells genetically modified with:	**lentiviral**	**5**
	Plasmid	**2**
	„synthetic“ DNA	**1**
	Bacterium (Plasmid transfected)	**4**
In vivo (51)	**mRNA**	**10**
	Adenoviral vector	**6**
	Plasmid	**6**
	„synthetic“ DNA	**1**
	Poxvirus vector (MVA, …)	**5**
	AAV	**8**
	Vaccinia or fowlpox (cond. replicating)	**7**
	HSV (cond. replicating)	**7**
	Onco-retrovirus repl. comp.	**1**

2005:	**2**
2006:	**5**
2007:	**10**
2008:	**6**
2009:	**3**
2010:	**2**
2011:	**7**
2012:	**9**
2013:	**6**
2014:	**7**
2015:	**16**
2016*:	**7**

Total: 80

Development of particular GTMP types in Germany

1) Oncolytic viruses:

A) Gene therapy medicinal products *(GMO):*

- genetically modified HSV *(2 products **(incl. Imlygic)**, 7 CTAs)*
- genetically modified vaccinia virus *(2 products, 5 CTAs)*
- genetically modified vaccinia combined with fowlpox virus *(2 CTAs)*
- genetically modified oncoretrovirus *(1 CTA)*

B) Not gene therapy *(wt or attenuated)*

- parvovirus *(1 product, 2 CTAs)*
- reovirus *(1 product, 1 CTA)*

Development of particular GTMP types in Germany

2) TCR-modified T-cells:

-CAR-T-cells *(4 products (anti-CD30, anti-CD19), 7 CTAs)*

-mTCR-T-cells *(1 product (anti-TA), 2 CTA)*

3) mRNA encoding TAA for tumour-immunotherapy

-application in vivo *(10 products, 10 CTAs)*

-modification of DCs ex vivo *(6 products, 6 CTAs)*
(classification as GTMP controversial)

4) Use of ZFNs, TALENs, CRISPR or Transposons for genetic modification of cells:

-Up to now no CTA, but increasing numbers of national Scientific Advices

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Regulatory activities to foster development of MPs in Europe

Specific for ATMPs:

CAT
(guidelines, classification, certification, scientific advice)

Hospital exemption

(for ATMPs prepared on a **non-routine basis in member state**,
used in a **hospital under the exclusive professional responsibility of a medical practitioner**,
custom-made product for an **individual patient**)

authorized by **member states**!

General (all types of medicinal products):

Conditional / accelerated / exceptional MA

Prime program

New clinical trial regulation (EU-centralisation)

Regulatory activities to foster development of MPs in Europe

Conditional marketing authorization

(if debilitating od life-threatening disease, emergency situations, or orphan disease)

- Positive risk-benefit relation, benefits tight risk
- Likely able to provide comprenesive data
- Unmet medical need
- Intended to end in regular marketing authorization in short time

Marketing authorization under exceptional circumstances

Provision of comprehensive data not possible due to:

- Number of patients too little
- Too low scientific knowledge
- Collection of data not possible dur to ethical reasons

Not intended to end in regular marketing authorization!
Specific obligations imposed, such as specific medical prescription, Study programs, or re-assessment

Regulatory activities to foster development of MPs in Europe

PRIME: Priority **Me**dicines

- Possible if unmet medical need, major therapeutic advantage

A rapporteur is appointed by CHMP or CAT early in the development
(as soon as promising data from initial clinical trials are available)

For micro-, small- and medium-sized enterprises and applicants from the academic sector: possible at earlier stage

Aim:
earlier scientific advice and regulatory support

Regulatory activities to foster development of MPs in Europe

Harmonization of Clinical Trials

In 2004: Implementation of the **Clinical Trials Directive** 2001/20/EC

EUDRA-CT: Data bank on clinical trials in EU (since 2004)

trials initiated before 2004 are not cited in EudraCT

for multinational clinical trials:

Initiation of a **Voluntary Harmonisation Procedure** (VHP)
(coordinated by **Clinical Trials Facilitation Group**, CTFG)

At present:
implementation of **new clinical trial regulation (EU 536/2014)**

New Clinical Trial Regulation

COUNCIL OF
THE EUROPEAN UNION

EN

Brussels, 20 December 2013
18127/13
(OR. en)
PRESSE 610

Council confirms agreement on clinical trials

The Permanent Representatives Committee[1] today approved a compromise agreed with the European Parliament on a draft regulation aimed at facilitating and speeding up the authorisation procedure of clinical trials. It herewith endorsed a compromise reached between the Lithuanian presidency and representatives of the European Parliament and of the Commission on 12 December.

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 April 2014

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Proposed New Clinical Trial Regulation

<u>Proposed</u> Changes (excerpt):

One single application via a single portal (managed by EC)

Harmonised dossier, Part I („general“) and Part II („national“)

One „reporting“ member state

Fix timelines

6 days selection of rMS
10 days validation *(+10 days for completion, +5 assessment of answers)*
45 days Assessment of Part I (+ 50 for ATMPs for expert consultation)
(26 days rMS, 12 days cMS, 7 days consolidation)
(31 days extention possible for questions, 12 days for answers)
12+ 7 days consolidation
in parallel: Assessment of Part II by concerned MS
5 days for final decision

Tacit approvals for MS that do not react in time

Enhanced transparency of study results

Beginning intended for

2018

Conclusion

GTMPs in Europe:

- a large number of different products under development
- for treatment of many different diseases
- promising product class, although only 3 products licensed up to now
- regulatory framework is (co)-evolving constantly
- several activities ongoing to foster development

Thank You for Your Attention

Thanks to

Brigitte Anliker
Klaus Cichutek
Egbert Flory
Matthias Renner
Ralf Sanzenbacher

Global Landscape of Commercialization of Stem Cell-based Therapeutics and Current Position of Korea

Miyoung Cho, Il-Hoan Oh

The Catholic University of Korea,

Center for Evaluating Next-Generation Stem Cell-based Therapeutics

Supported by MFDS, but not reflecting current opinion of MFDS

Topics

- **Global Landscape of Commercialization**
  : based on the analysis of industry-sponsored clinical trials
- **Current Position of Korea**
  : in the context of R&D activity and regulatory system

Approved products

Product	Hearticellgram-AMI	Cartistem	Cupistem	Prochymal	Neuronata-R	Holoclar	Temcell HS	Heartsheet
Company	Pharmicell	Medipost	Anterogen	Osiris	Corestem	Chiesi	JCR	Terumo
Approved year	2011 Jul	2012 Jan	2012 Jan	2012 May	2014 Aug	2015 Feb	2015 Sep	2015 Sep
Country	Korea	Korea	Korea	Canada, NZ	Korea	EU	Japan	Japan
Indication	AMI	Knee Cartilage defect	Anal fistula	Acute GvHD	ALS	Limbal stem cell deficiency	Acute GvHD	Heart failure
Cell type	Auto BM-MSC	Allo CB-MSC	Auto Adipose-MSC	Allo BM-MSC	Auto BM-MSC	Auto corneal epithelial cells	Allo BM-MSC	Auto myoblast sheet
Approval type	Full (f/u required)	Full (f/u required)	Conditional	Conditional	Conditional	Conditional	Full	Conditional

Clinical trials for commercializing stem cell-based therapeutics

ClinicalTrials.gov
Protocol Registration System

Final Analysis Set
(as of 31 Dec, 2015)

317
Stem-cell based intervention study

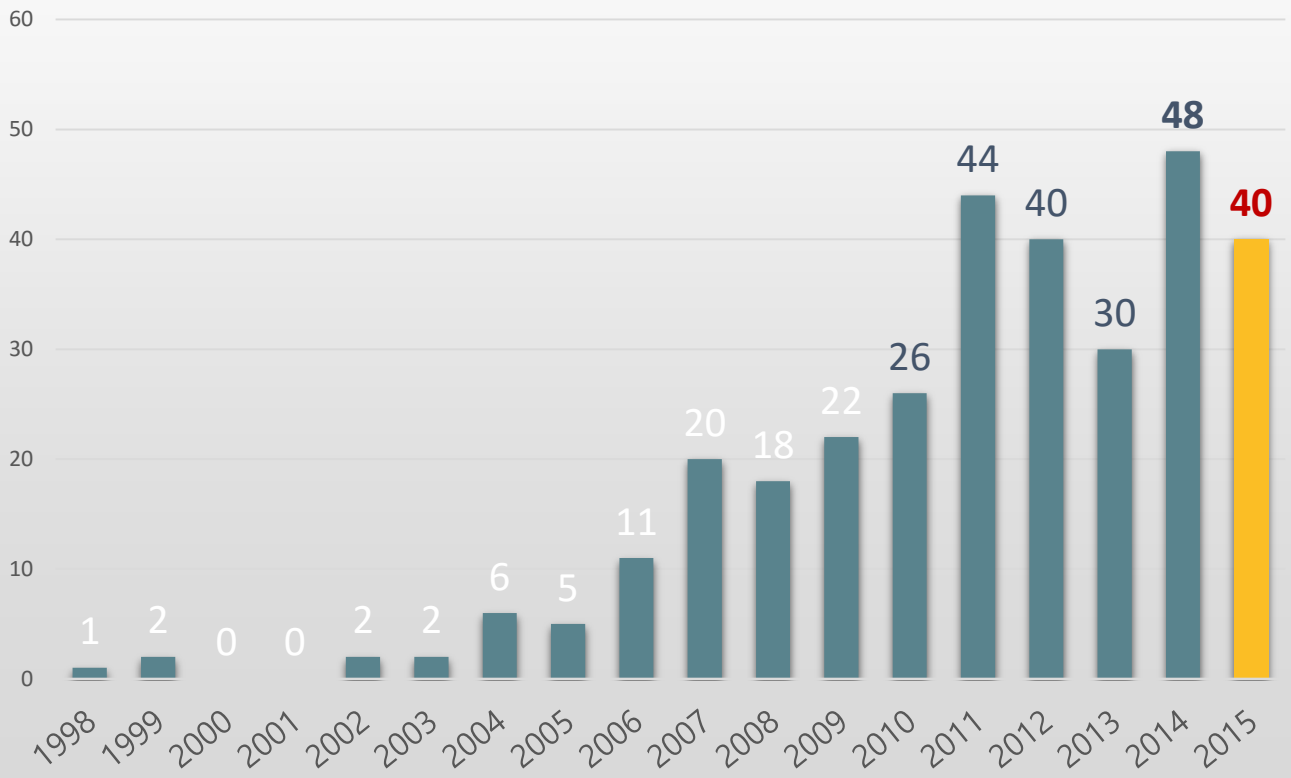
1,342
"Industry-sponsored" by category

5,400
"Stem cell" key word

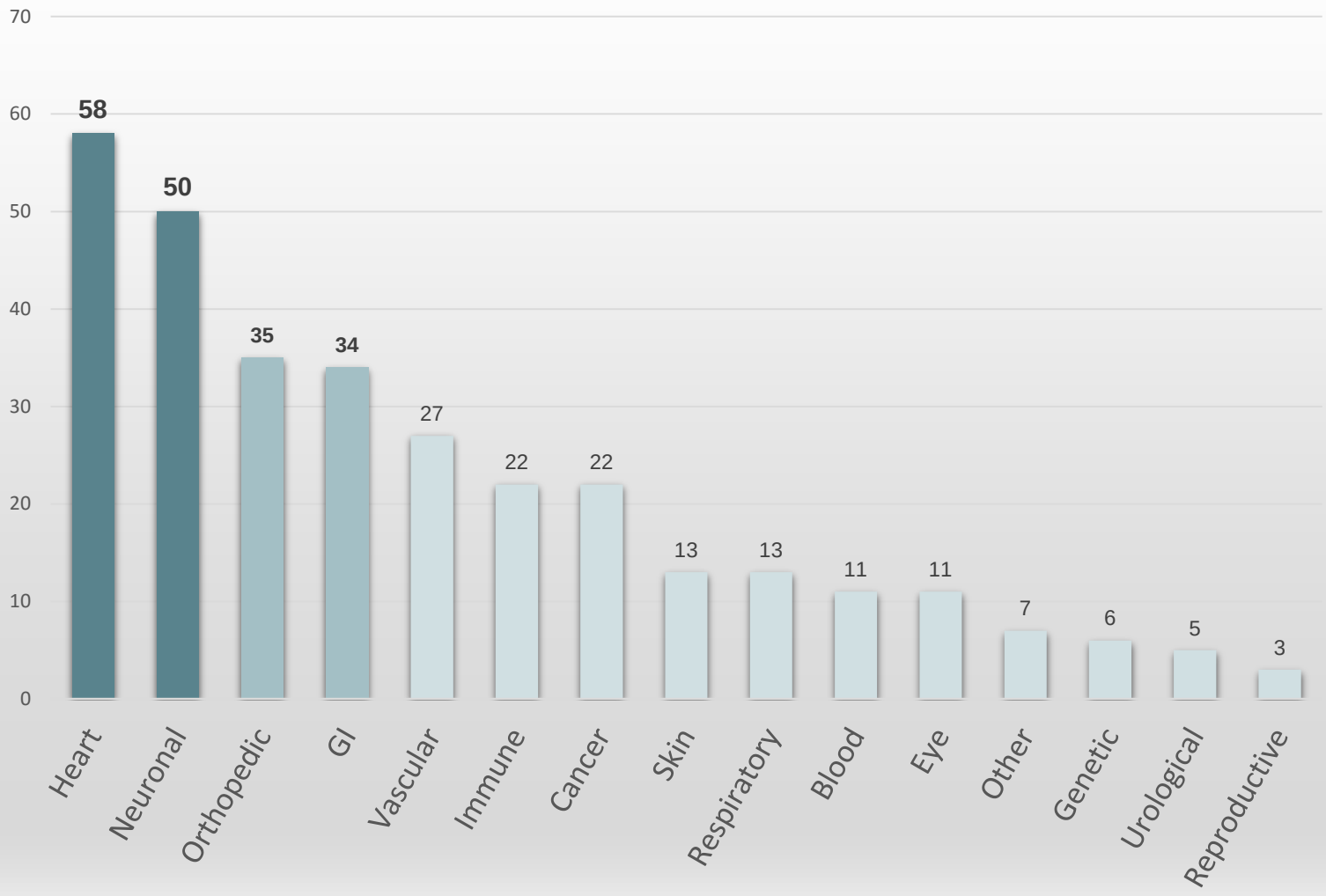
This analysis is solely based on the **'registered information'** which is claimed by the sponsors, and therefore may include some unintentional errors by its nature.

#Reference: 줄기세포치료제 개발 및 규제동향 2015

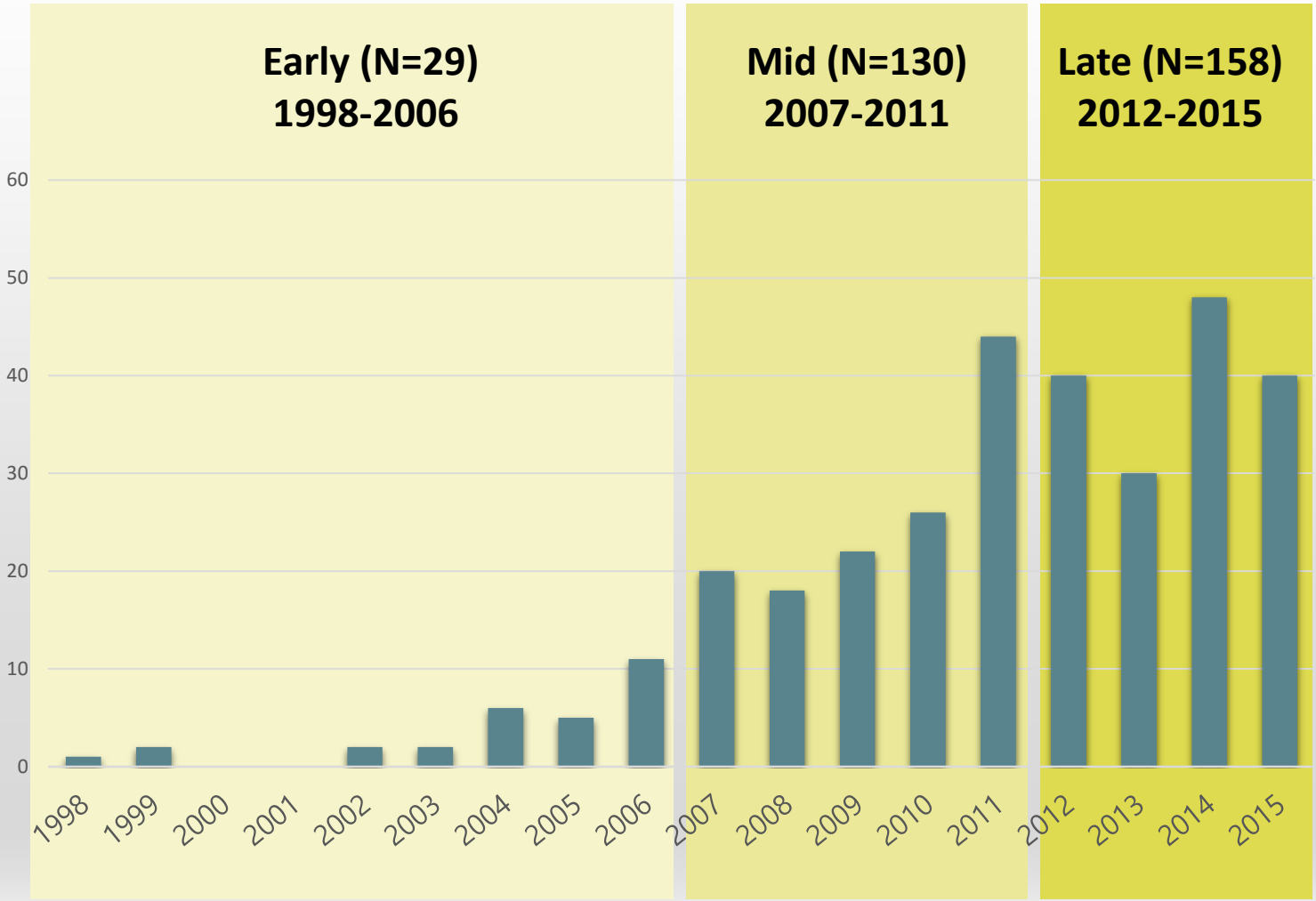
Number of clinical trials



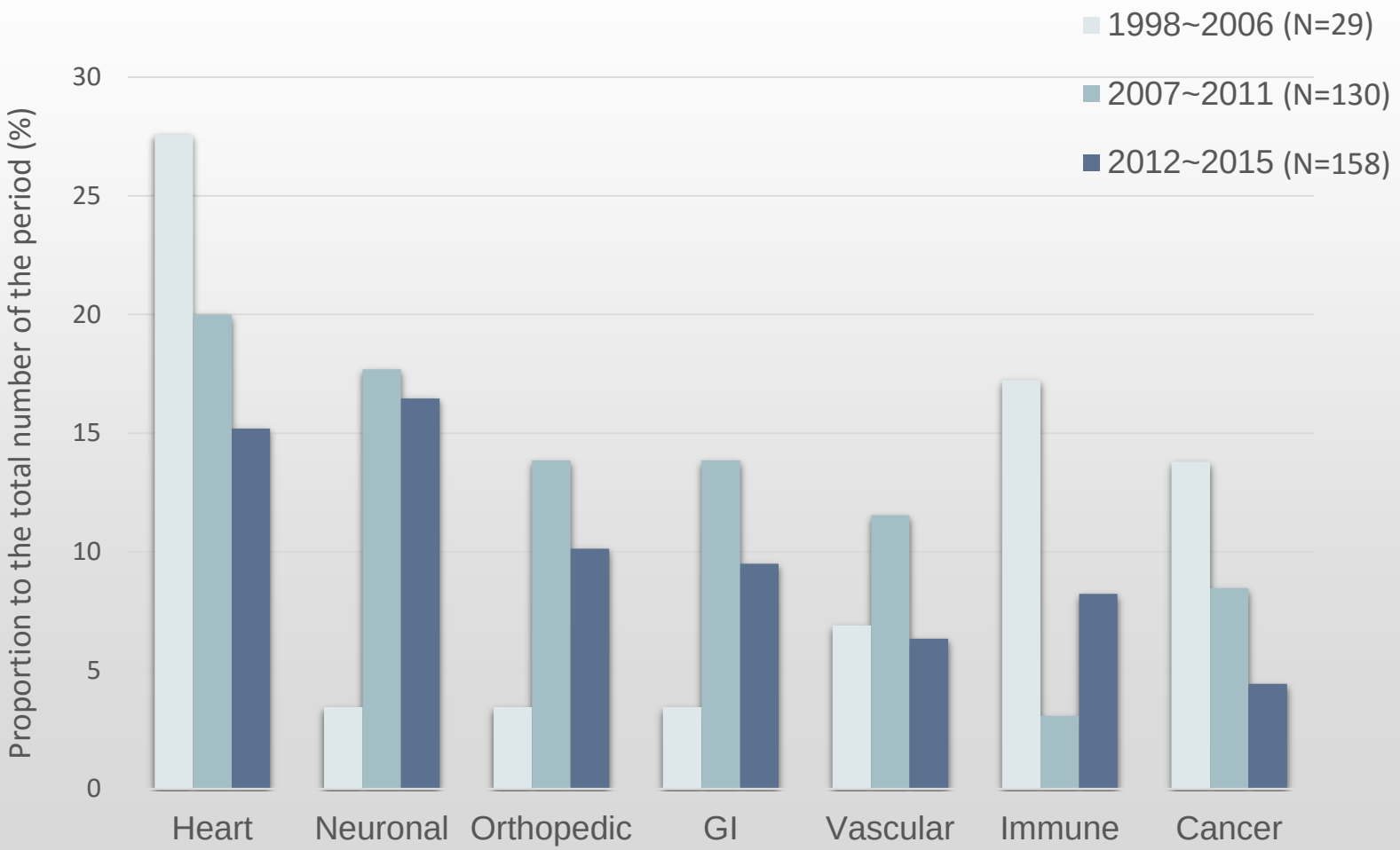
Target diseases



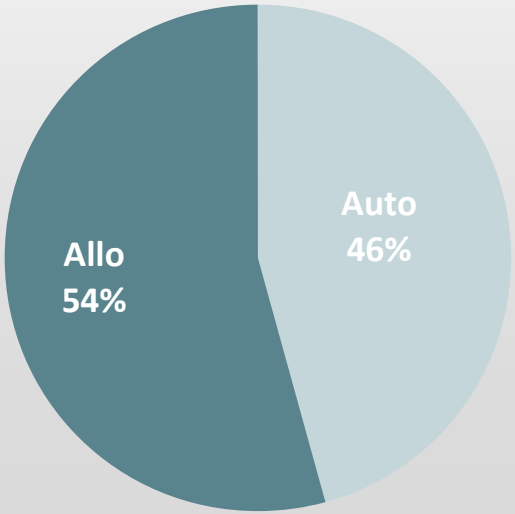
Sub-analysis set

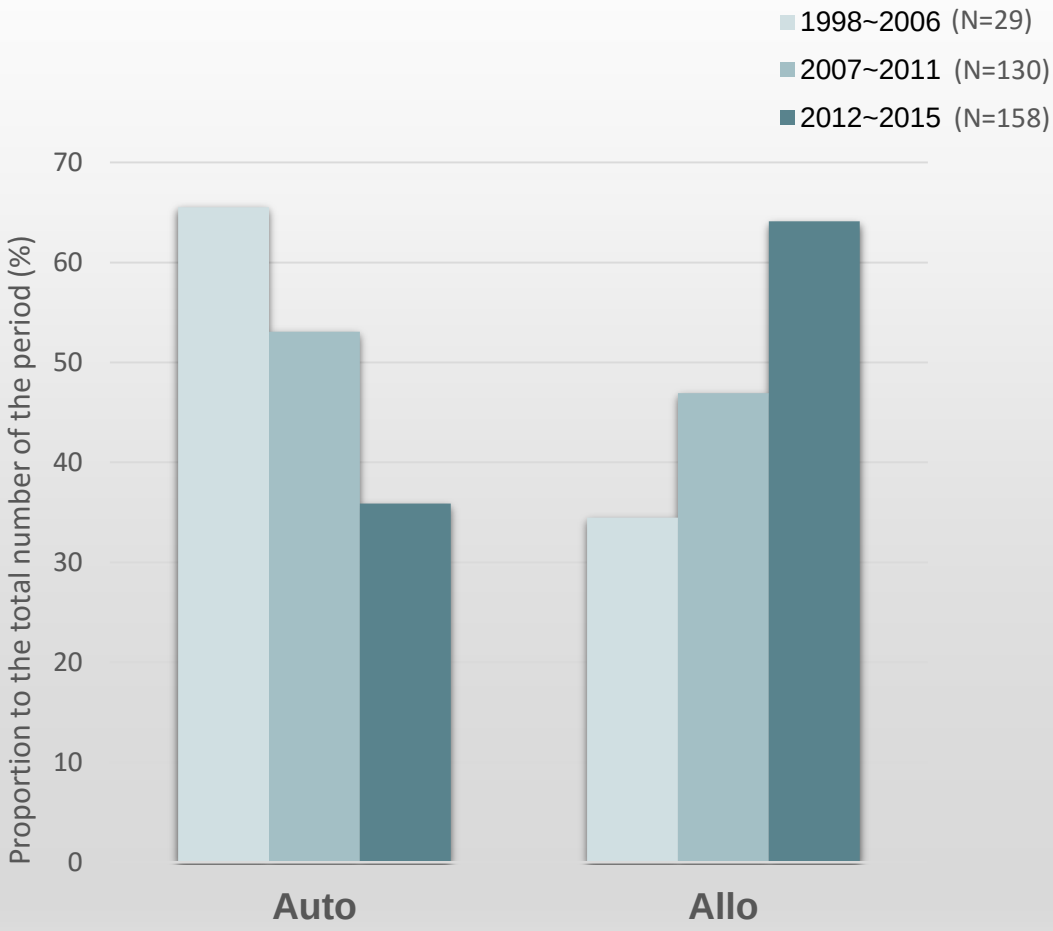


Changes in target disease

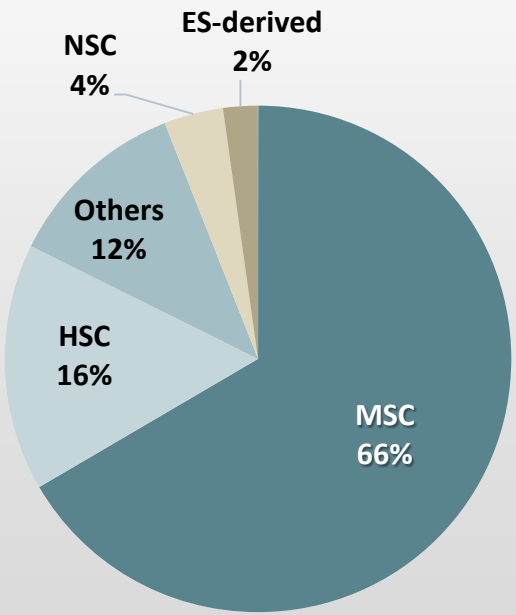


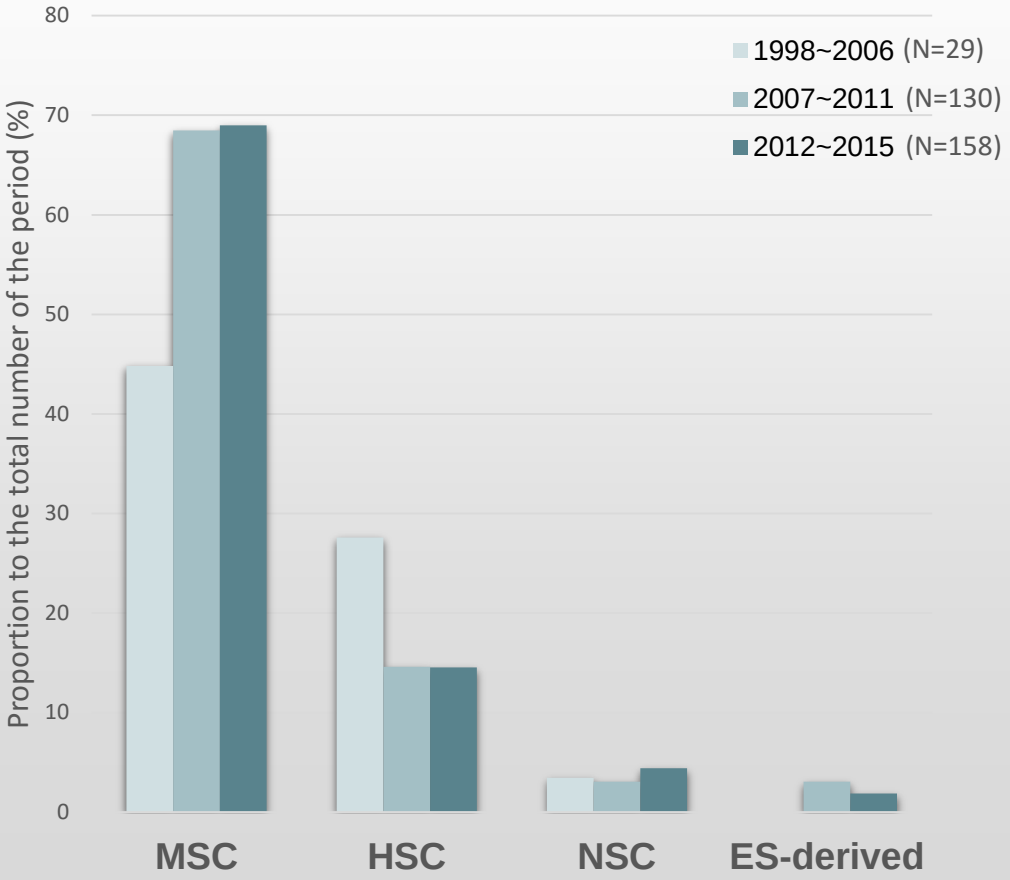
Cell source (Autologous vs. Allogeneic)



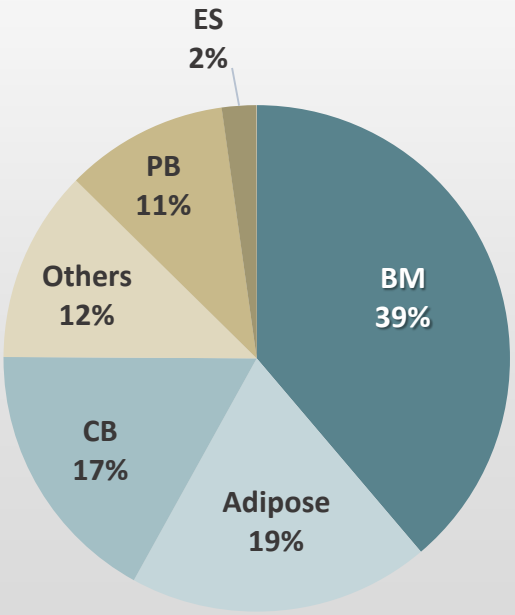


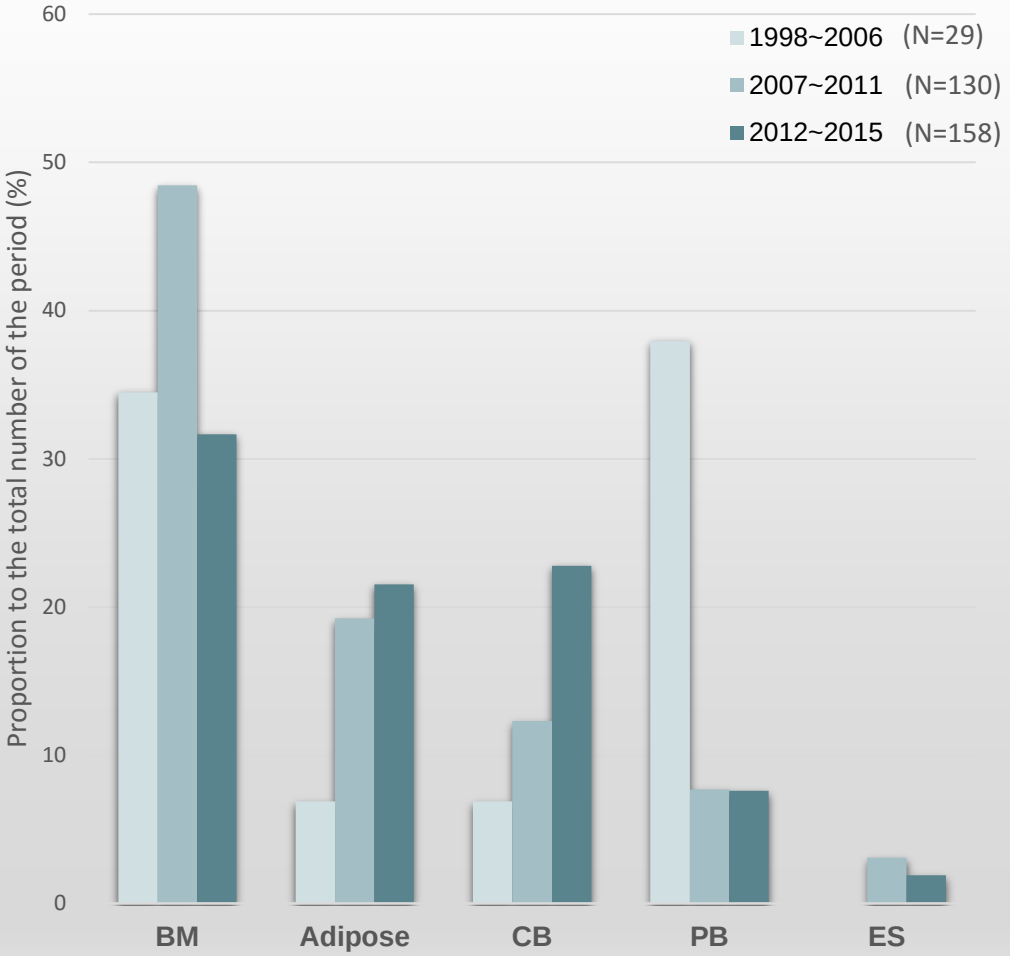
Cell type


ES-derived
2%
NSC
4%
Others
12%
HSC
16%
MSC
66%

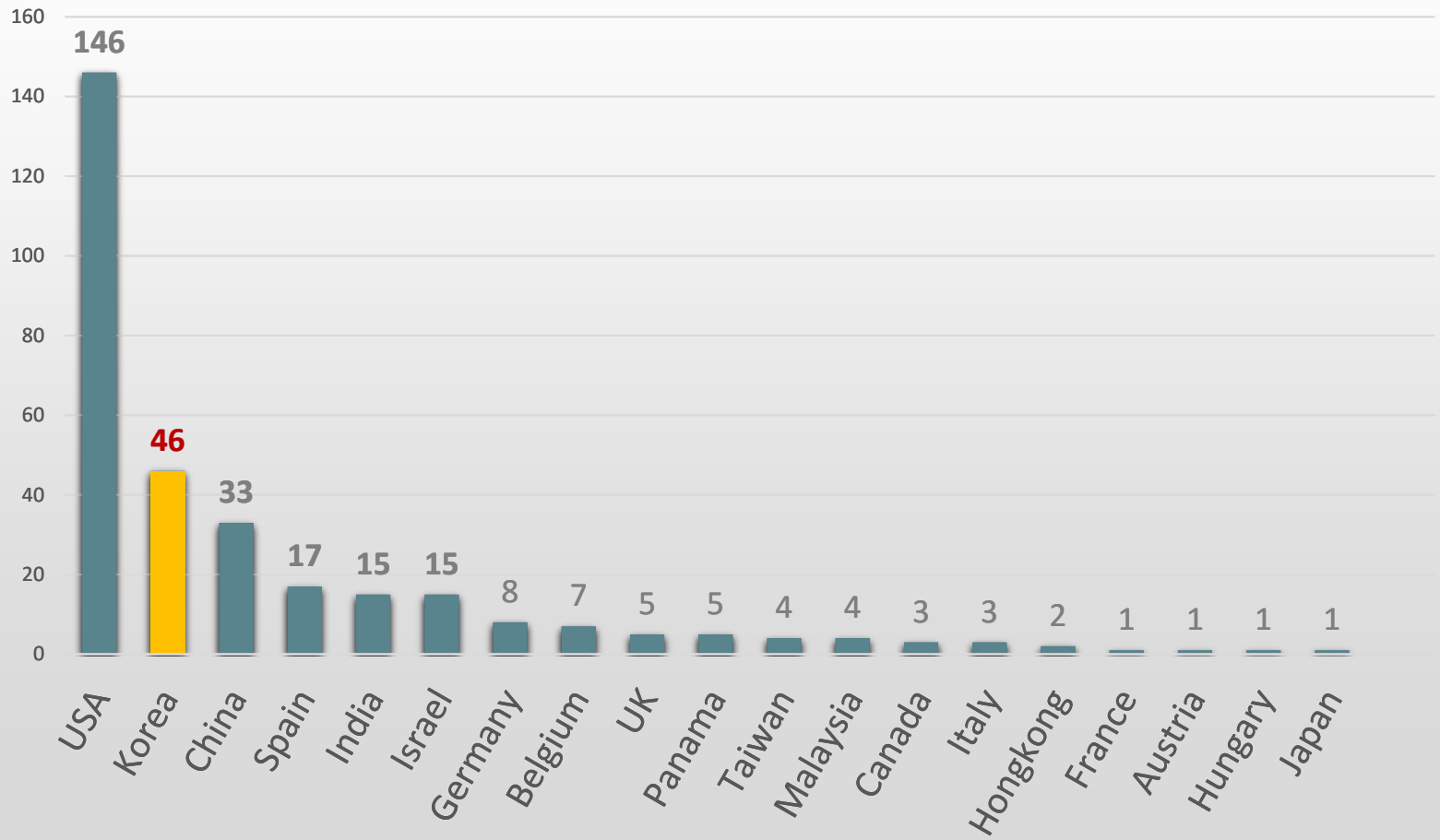

80
70
60
50
40
30
20
10
0
Proportion to the total number of the period (%)
1998~2006 (N=29)
2007~2011 (N=130)
2012~2015 (N=158)
MSC
HSC
NSC
ES-derived

Tissue origin

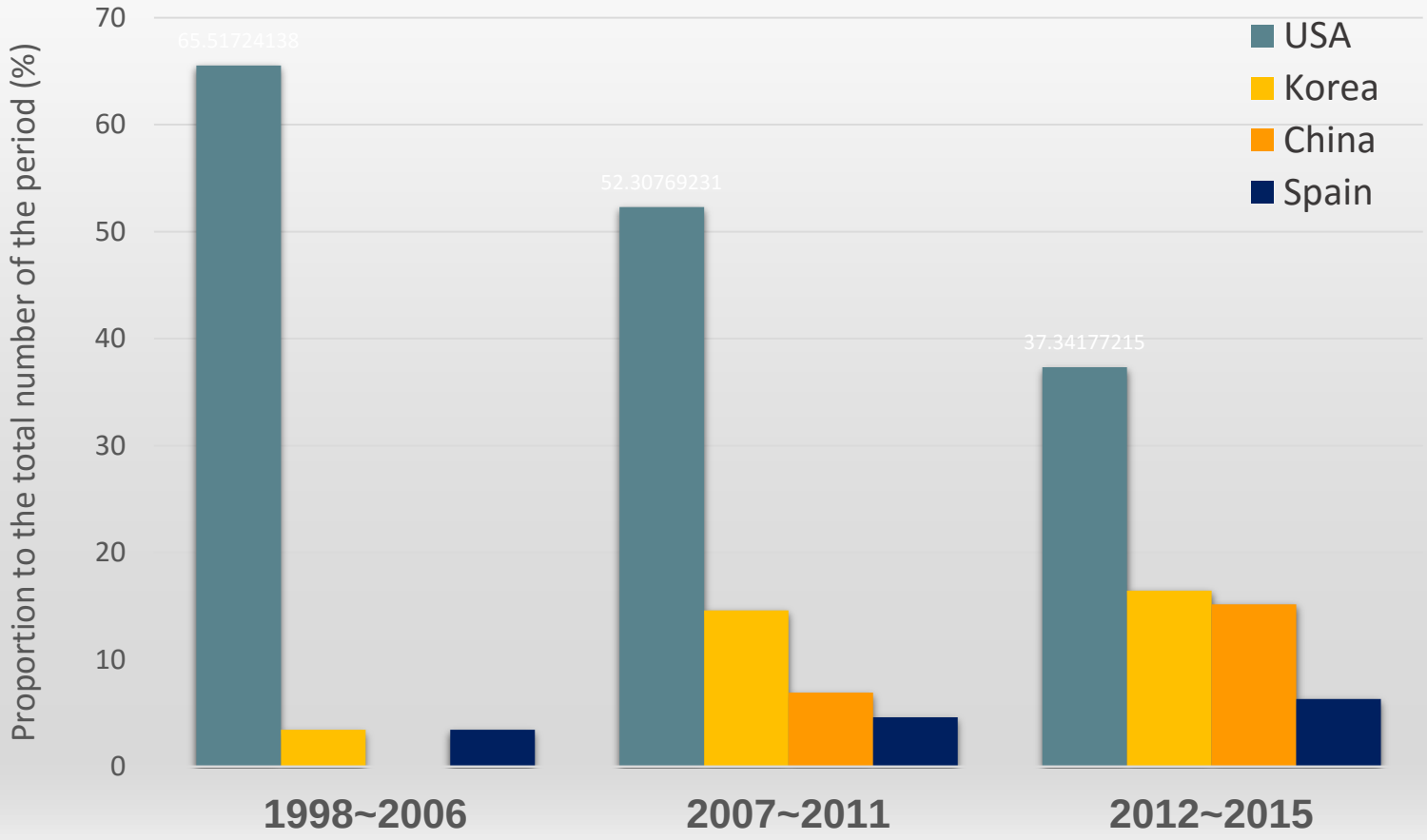




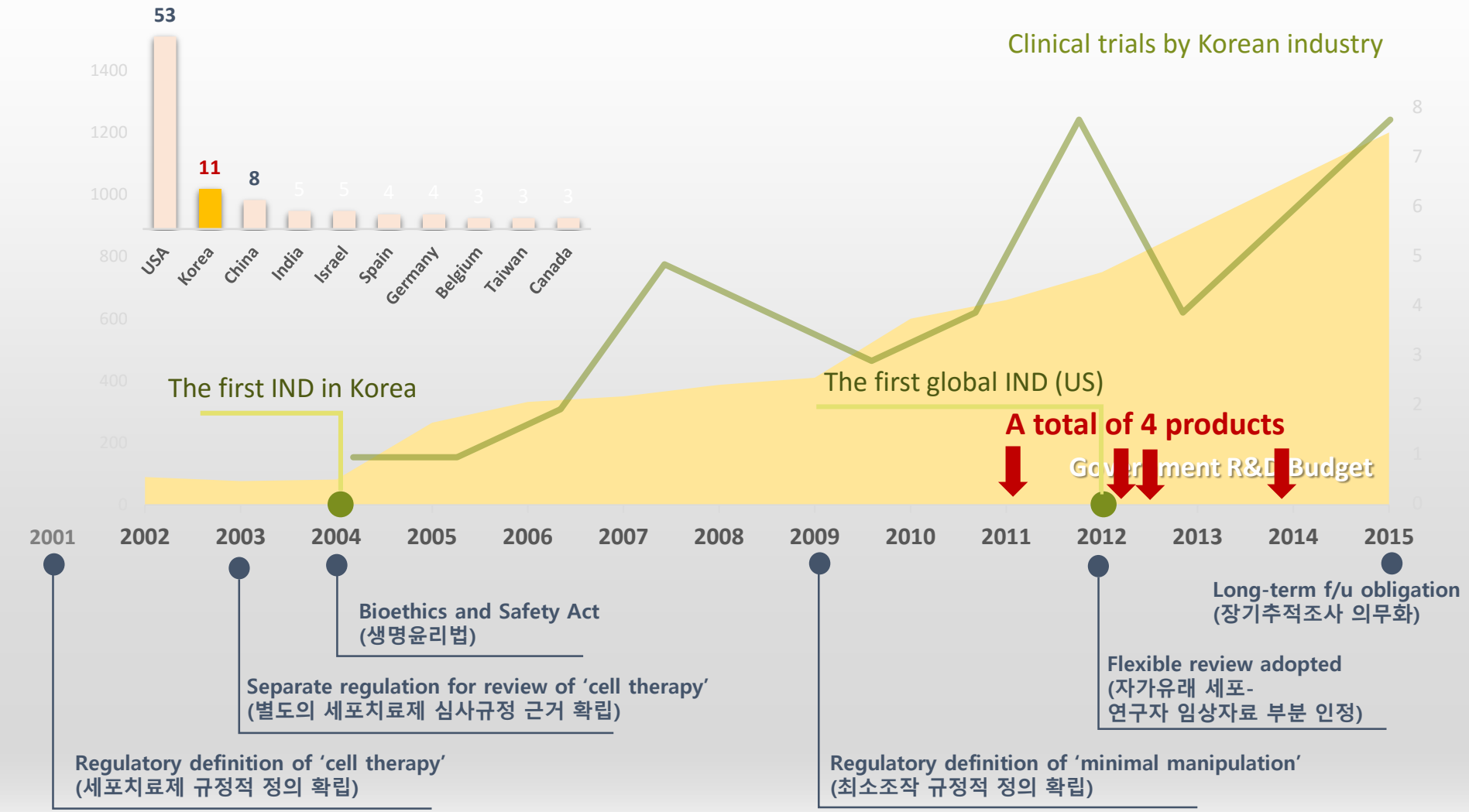
Share by country



Changes in share



How could this possible?



Thank you

GBC 2016 Jun28, 2016

Update on Regulatory Aspect of Regenerative Medicine, and on Cellular and Gene Therapy Products in Japan.

Masakazu Hirata, MD PhD

Office of Cellular and Tissue-based Products and Division of Pharmaceutical Consultation (Kansai Branch)

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Disclaimer

The views and opinions expressed here are those of the presenter and do not necessarily represent those of the PMDA.

Regulatory authorities in Japan (1)

Ministry of Health, Labor and Welfare (MHLW)

Planning health policy and enforcing administrative measures based on the law

ex.
- To give marketing authorizations
- To Issue emergency safety information
- To direct product withdrawal/recall
- To take safety measures for emergent and significant cases

Regulatory authorities in Japan (2)

Pharmaceuticals and Medical Devices Agency (PMDA)

Review, examination, data analysis

- Scientific review
- GMP/GLP/GCP/GCTP inspections
- Consultations for marketing authorization
- Collection, analysis and dissemination of information regarding quality, efficacy and safety

Recent Changes in Regulation

Regenerative medicine & cell therapy in Japan (Past)

The Act on the Safety of Regenerative Medicine

Pharmaceuticals and Medical Devices Act (PMD Act)

Academic Research

Products for Marketing Authorization

Medical care

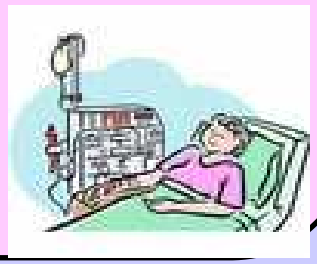
Unknown numbers
No Specific oversight

Six types of therapy were provided in approved research hospitals as "advanced care"
* Partially covered by natl health insurance

Clinical Research using human stem cells (under the Guideline for Human Stem Cell Clinical Research - since 2006)

108 protocols approved
(as of November 2014)

Cancer immunotherapy

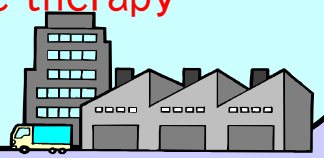


Cellular/Tissue based Products

2 approved products
- JACE (autologous cultured epidermis)
- JACC (autologous cultured cartilage)

2 products under review Process

19 clinical trials initiated (including 5 gene therapy products)
(～January 2015)



Solely by MHLW

Regulated by PMDA

Stem cell clinical research approved in Japan(as of May 2014)

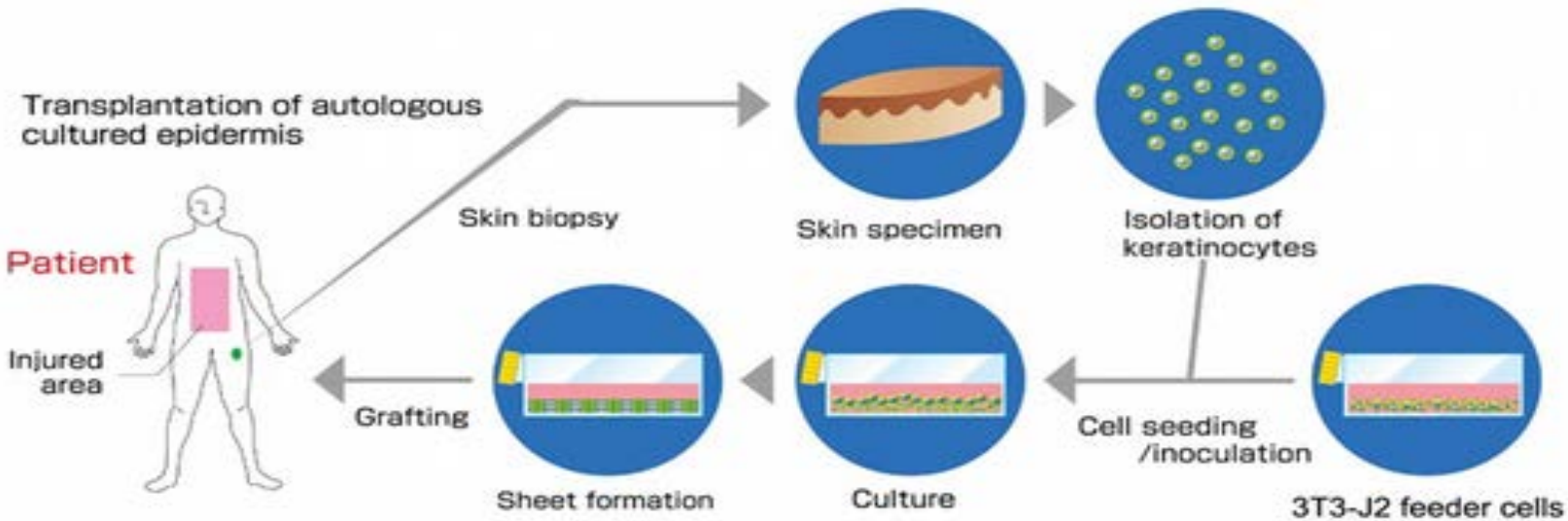
Source	Origin	No. of Institution
Adipose Tissue	autologous	10
Bone Marrow	autologous	27
Bone Marrow	allogeneic	2
Cord Blood	autologous	1
Corneal Epithelium	autologous	1
Corneal Endothelium	allogeneic	1
Corneal Tissue	allogeneic	2
Dental Tissue	autologous	3
Myocardium	autologous	3
Nasal Epithelium	autologous	1
Oral Mucosa	autologous	9
Periosteum or Chondrocyte	autologous	2
Peripheral Blood	autologous	20
Skeletal Muscle	autologous	3
Synovial Tissue	autologous	4
IPS Cells	autologous	2

Two authorized products under PAL(1/2)

Autologous Cultured Epidermis ***JACE***

- Submission: 6th Oct. 2004
- Marketing authorization: 29th Oct. 2007

JACE



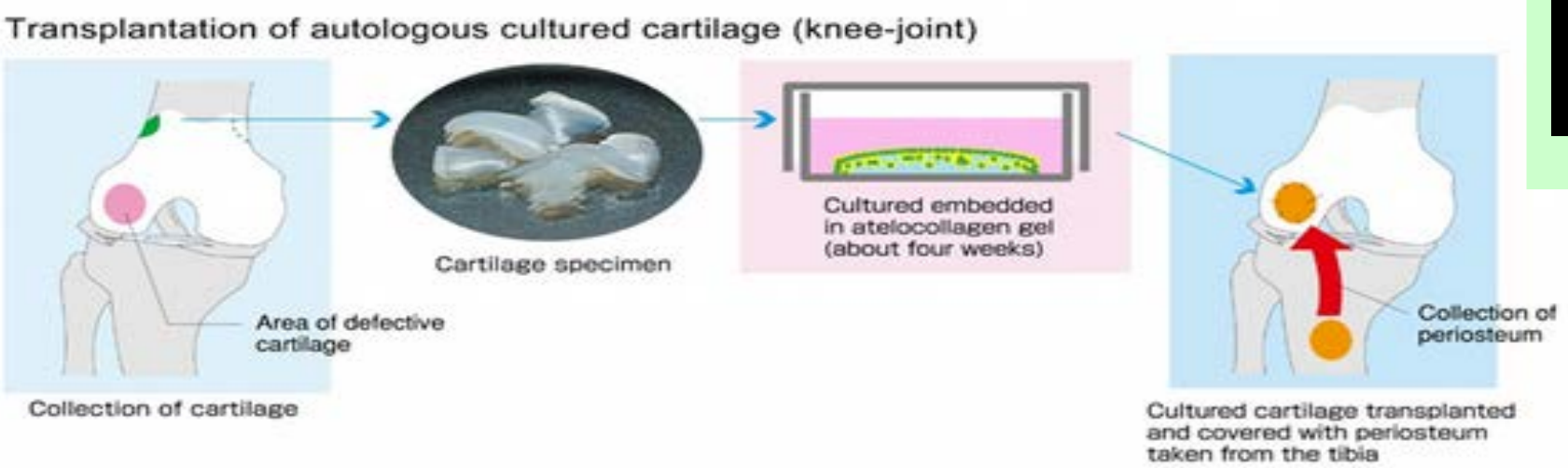
Ref. Japan Tissue Engineering Co. Ltd. HP

- Indication: serious burns treatment (>30% of the body surface area)

Two authorized products under PAL(2/2)

Autologous Cultured Cartilage ***JACC***

- Submission: 24th Aug. 2009
- Marketing authorization: 27th July 2012



Ref. Japan Tissue Engineering Co. Ltd. HP

- Indication: Relief of symptoms of traumatic cartilage defects and osteochondritis dissecans (excluding OA) for knee joints (>4cm^2 lesions with no alternative therapies)

Two Acts regulating regenerative medicine & cell therapy

MHLW process

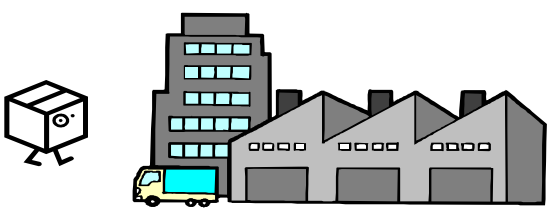
Regenerative Medicine

PMDA process

* Two laws were enacted on 25 November 2014

All medical **technologies** using processed cells which safety and efficacy have not yet been established

Production and marketing of regenerative and cellular therapeutic **products** by firms



The Act on the Safety of Regenerative Medicine

It may be similar to Hospital exemption of the EU or PHS 361 in the US

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

New Legislative Framework

These two acts were promulgated in November 2013 by the Japanese Diet (Parliament) in line with the **Regenerative Medicine Promotion Act**, in order to reform the pharmaceutical and medical regulation related to regenerative medicine

- **Revision of the Pharmaceutical Affaires Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act)**

- The Act on the Safety of Regenerative Medicine

These two acts were enacted on 25 November 2014

Other related governmental policy:

- **Healthcare and Medical Strategy Promotion Act (2014.5)**
- **Japan Medical Research Development Institution Act (2014.5)**

Overview of the Act on the Safety of Regenerative Medicine

Provision of regenerative medicine

I. Obligate hospitals and clinics to submit plans

Hospitals / Clinics

II. Enable commissioning cell processing to licensed enterprises

Cell processing

Certified committee for regenerative medicine

Certification

Cell processors

III. Obligate CPCs to notify or obtain licence

MHLW

Notification (Hospitals / Clinics) or
Application for a license (Firms)

So far 41 facilities have got licensed

Two acts regulating regenerative medicines

Regenerative Medicines

All medical technologies using processed cells which safety and efficacy have not yet been established

Act on the Safety of Regenerative Medicine

Production and marketing of regenerative and cellular therapeutic products by firms

Pharmaceuticals and Medical Devices Act (PMD Act)

Both enacted in November 2014

Regenerative medicine & cell therapy in Japan

Medical Care Act (MCA) = The Act on the Safety of Regenerative Medicine.

Pharmaceuticals and Medical Devices Act. (PMD Act.)

Academic Research Purpose

Commercial Product Marketing Authorization Purpose

Medical care

Clinical Research using human stem cells

108 protocols approved

(as of November 2014 – before new legislation)

Under the new legislation, as of 31 January 2016:

79 new clinical research plans,

2634 medical care plans

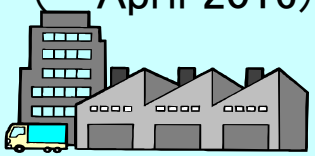
have been notified to MHLW

Regenerative Medical Products

4 approved marketed products

33 clinical trials initiated (including 9 gene therapy products)

(～April 2016)

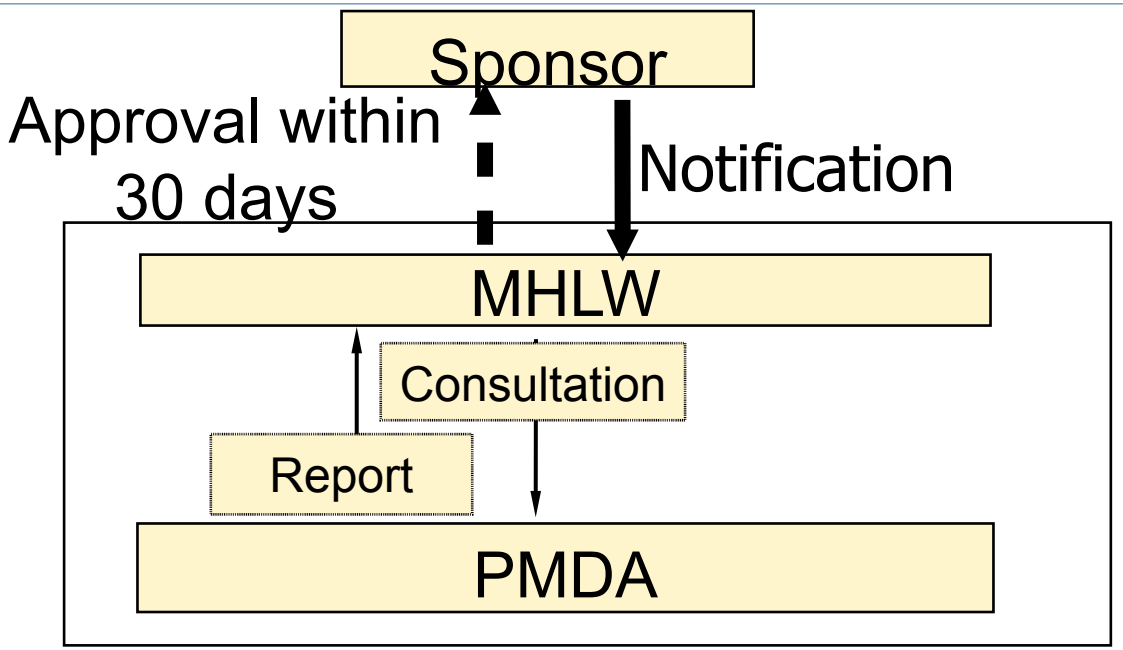


Covered by MHLW

Covered by MHLW and PMDA

Regulations of Gene Therapy Clinical Trials in Japan

Clinical Trials under Pharmaceuticals and Medical Devices Act



Guidelines for Assuring the Quality and Safety of Gene Therapy Products

Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organism (Cartagena Law) (2004)

Type 2 Use for manufacturing investigative medical products
Type 1 Use for administration to human

Regenerative Medicine Products in the PMD Act

Pre 2014: Pharmaceutical Affairs Law (PAL)

Drug

Device

PMD Act (Revised PAL)

Drug

Regenerative Medical Products

Device

- **New Additions for Regenerative Medicine Products**
  - Definition and independent chapter for Regenerative Medicine Products
  - Introduction of conditional/time limited approval system

Definition of “Regenerative medical products” in PMD Act

Regenerative medical products are defined as:

1. Processed human or animal cells that are intended to be used for either

(1) reconstruction, repair, or formation of structures or functions of the human body, or

(2) treatment or prevention of human diseases,

→ **Regenerative Medicinal Products, Cell Therapy Products**

2. Products for gene therapy.

→ **Gene Therapy Products**

≃ Cellular and Tissue based Products and Gene therapy Products

≃ Advanced-therapy medicinal products (ATMPs) Regulation (EC) No 1394/2007

Scope of Manipulation ("Processed cells") to be regulated

(Definition)

1. **Manipulation to be regulated**
   - artificial proliferation and differentiation of cells and tissues
   - cell lines established
   - drug treatment for the purpose of activation
   - biological properties modification
   - combination with non-cellular components
   - genetic engineering modification
   - Isolation/separation of specific cell by biological and chemical treatment with agents
   - Cell for non-homologous use
2. **Minimal manipulations** such as, treatment with antibiotics, washing, freezing, The gamma ray sterilization, simple isolation/separation without biological and chemical treatment **are not covered by the new regulation**

Blood transfusion (blood products), Hematopoietic stem cell transplantation, Assisted Reproductive Technology, except those derived from genetic engineering, iPS cells, are also excluded from the scope of the regenerative medicine regulation.

Limitations of Clinical Trials of Regenerative Medicine to satisfy unmet medical needs

There are some specific limitations for cell therapy products

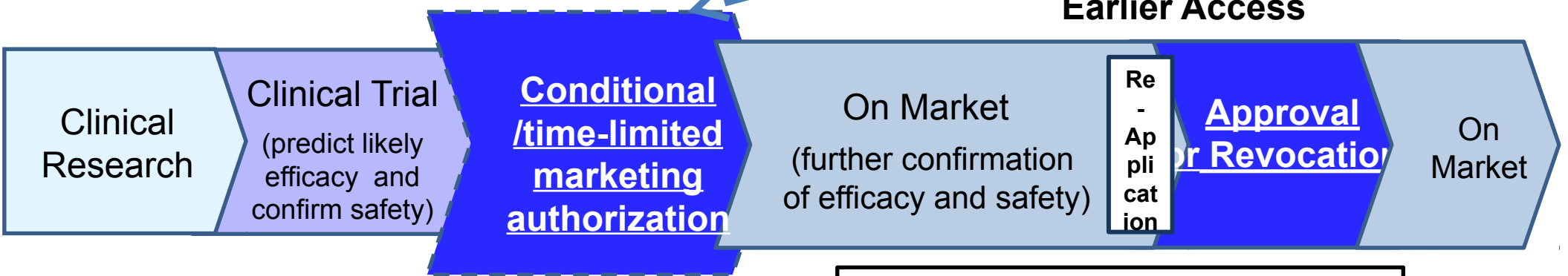
- Designed for unmet needs under the present treatment (e.g. last line therapy): limited number of patients available for clinical trials
- Difficult to conduct controlled study to demonstrate clinical benefit, in the Japanese medical environment, due to:
  - highly invasive surgical intervention
  - autologous cell collection
- Clinical trial design affected by heterogeneity of quality derived from source materials (including autologous collection and culture procedures)

Expedited approval system under PMD Act

【Standard Pathway of Approval for Drugs and Regenerative Medicinal Products】

【New Pathway for Regenerative Medical Products】

※ **Leading to Earlier Access**



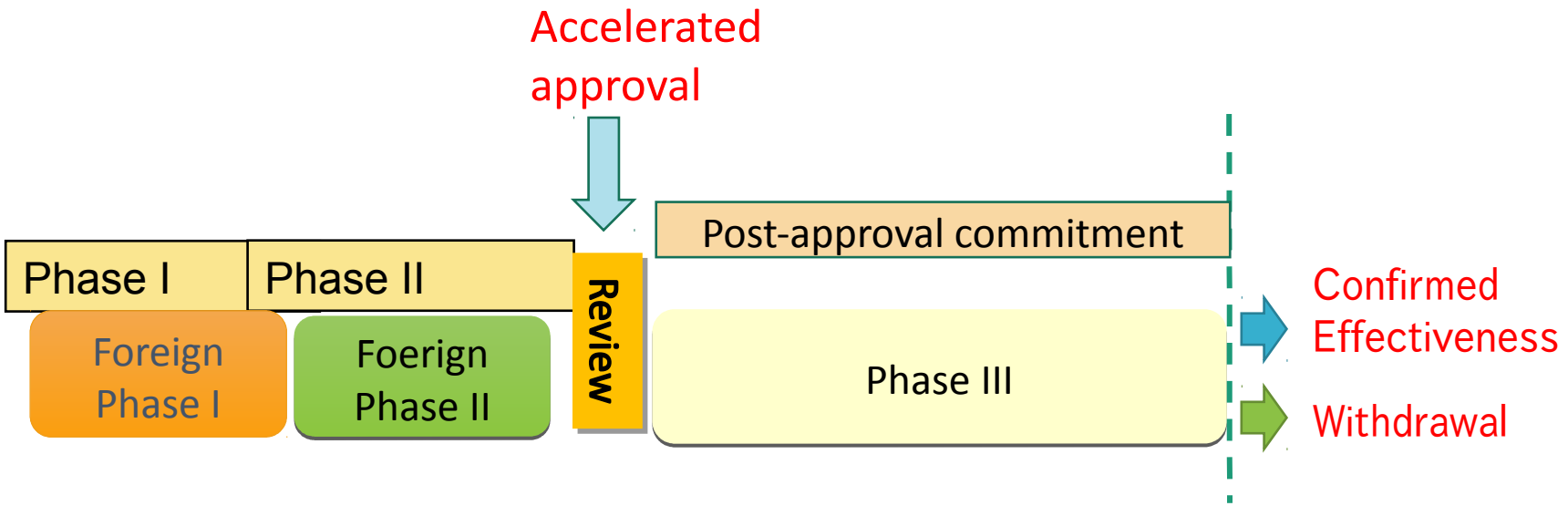
Post-marketing safety measures plus explicit informed consent from patients

Evolving Early Access schemes of ICH founding 3 regions

Each agency has similar approaches to accommodate patient access demand.

Type	US	EU	JAPAN
priority	Priority Review Orphan Designation	Accelerated review Orphan Designation	Priority review Orphan Designation
Conditional	Accelerated approval for serious or life- threatening illnesses	Conditional MA MA under exceptional circumstances **Pilot Project on Adaptive path (new)**	Approval for Oncology drug, Orphan drug **Conditional & Time-limited approval for regenerative medicine (new)**
Rolling submission	Break through therapy & Fast Track designation	**PRIME (new)**	**Forerunner Review Assignment (new)**

US Accelerated approvals and development



(drugs for life-threatening disease and unmet medical needs)

- To approve products based on the limited data, such as surrogate endpoints in exploratory study.
- Similarity to accelerated approval of USFDA * The product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (ref.)

Ref.) USFDA--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (57 FR 58958, Dec. 11, 1992)

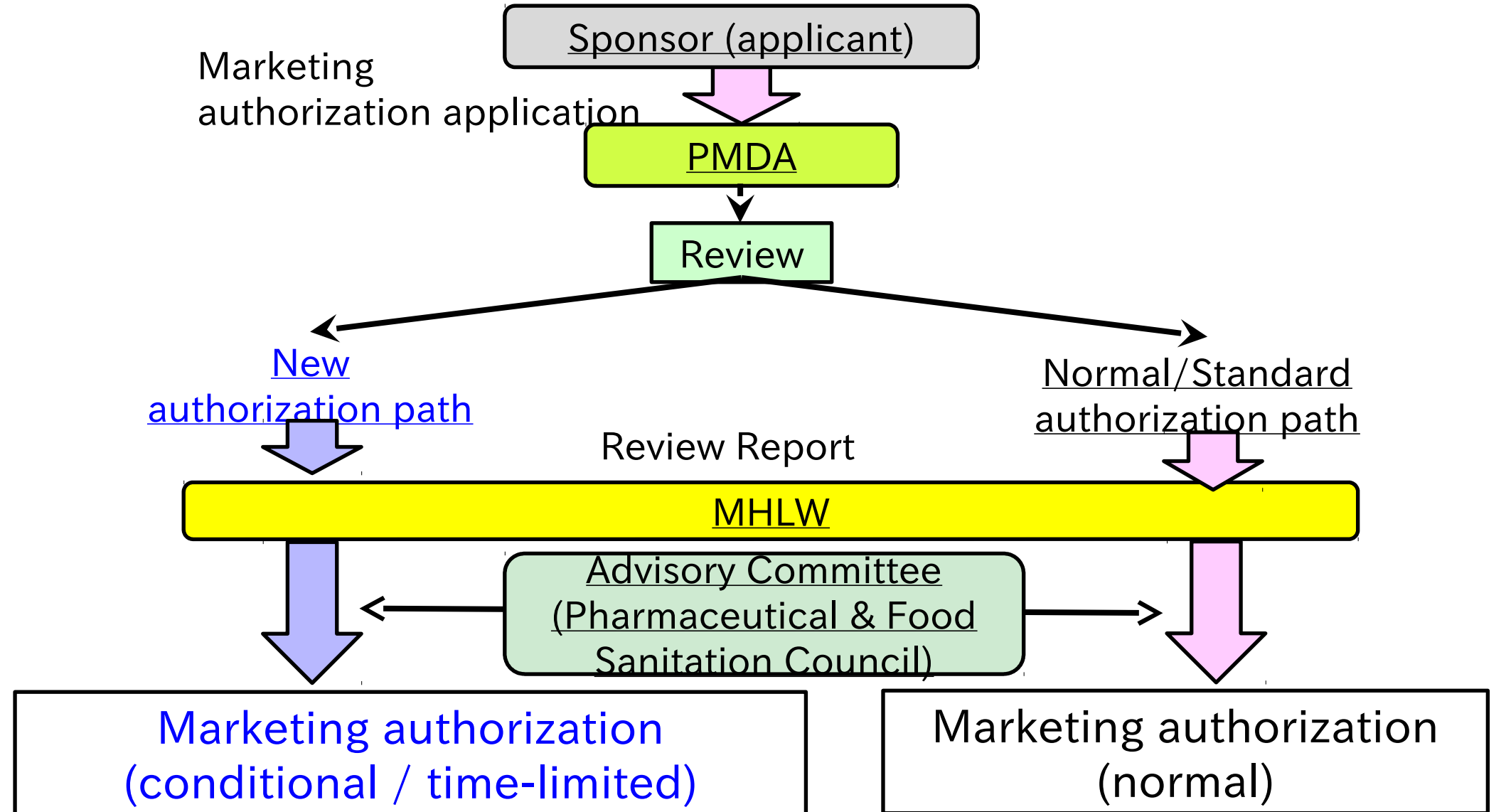
Efficacy under conditional /time-limited approval

Efficacy has not been fully determined, but

“Reasonably likely to predict clinical benefit approach”
may be taken in the review process
under Conditional /time-limited authorization path
of regenerative medical products

cf.) US Food Drug and Cosmetics Act--Accelerated Approval of New Drugs
for Serious or Life-Threatening Illnesses
(57 FR 58958, Dec. 11, 1992)
and adopted in Food Drug and Cosmetic Act Sec. 506

Review pathway of regenerative medical products under the PMD Act

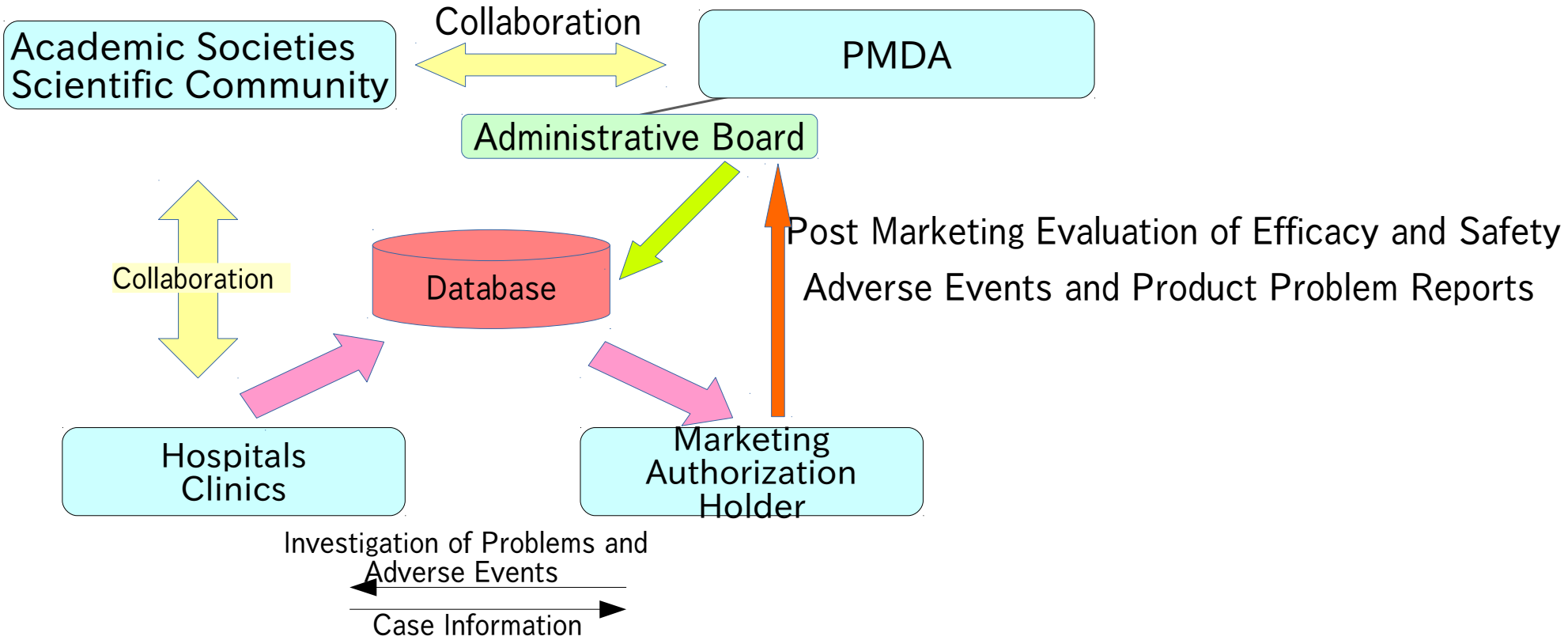


Public no-fault Indemnity system for patient injuries associated with products approved under PMD Act.

	Biological device	Regenerative medical products
Conditional and time limited approval	NA	√
Adverse Drug Reaction Relief Fund	NA	√
Infection Relief Fund	√	√

Private Insurance products will be available for clinical studies under the Act on the Safety of Regenerative Medicine

Patient Registry System for Regenerative Medical Products (Planned)



Further acceleration……

Strategy of SAKIGAKE
(Forerunner review assignment system)

厚生労働省

Strategy of SAKIGAKE

(Japanese)

The Ministry of Health, Labour and Welfare (MHLW) has formed the "Strategy of SAKIGAKE" by Ministry Project Team to lead the world in the practical application of innovative medical products (Press release (in Japanese)) This PT has been launched to plan strategies as a package covering from basic research to the practical application with related divisions within the MHLW.

The Strategy of SAKIGAKE consists of two measurements as follows and covers from basic research to clinical research/trials, approval reviews, safety measures, insurance coverage, improvement of infrastructure and the environment for corporate activities, and global expansion.

- SAKIGAKE Designation System: promoting R&D in Japan aiming at early practical application for innovative pharmaceutical products, medical devices, and regenerative medicines
- Scheme for Rapid Authorization of Unapproved Drugs: accelerating the practical application of unapproved/off-label use of drugs for serious and life-threatening diseases by expanding the scope of the Council on Unapproved Drugs/Off-label Use to include unapproved in Western countries if it satisfies certain conditions and by improving the environment for companies to undertake development of such drugs

The MHLW will implement these policies during the budgetary request process in FY2015, but some of them which are ready will be executed in 2014 ahead of schedule.

<Materials>

- Strategy of SAKIGAKE (PDF:379KB)
- Summary of Strategy of SAKIGAKE (PDF:587KB)

- MHLW drew up a new strategy to lead the world in the practical application of innovative medical products in 2014.

http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html

SAKIGAKE Designation System

– To put innovative products into practice in Japan first in the world –

Designation Criteria

- Medical products for diseases in dire need of innovative therapy
- Applied for approval firstly or simultaneously in Japan
- Prominent effectiveness can be expected based on non-clinical study and early phase of clinical trials

Designation Advantage

1. Prioritized Consultation [Waiting time: 2 months→1 month]
2. Substantialized Pre-application Consultation [de facto review before application]
3. Prioritized Review [12 months → 6 months]
4. Review Partner [PMDA manager as a concierge]
5. Substantial Post-Marketing Safety Measures[Extension of re-examination period]

Designation Procedure

1. Initiation by applicant 2. Initiation by the MHLW

Assignment on 10 February 2016 regenerative medical products

Name of medical products	Proposed indication	Name of applicant
STR01 (Autologous bone marrow-derived mesenchymal stem cell)	Nerve syndrome and dysfunction caused by spinal cord injury	NIPRO Medical Co., Ltd. /Sapporo Medical Univ.
G47△ (Growth-controlled oncolytic herpes simplex virus type 1)	Malignant glioma	Daiichi Sankyo Co., Ltd. / Institute of Medical Sciences, University of Tokyo
autologous cardiac progenitor/stem cells	Pediatric congenital heart disease (single ventricle physiology)	Japan Regenerative Medicine Co., Ltd. /Okayama University

Examples of Product review

(specific points to consider for cellular therapy products)

Two of the new product approvals under the new regulation (Update)

- In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.
- They were approved on 18 September 2015.

1. Bone marrow mesenchymal stem cells (MSCs) for GVHD **(normal approval)**
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease **(conditional and time-limited authorization** – 5 years, conducting post-marketing efficacy studies**)**

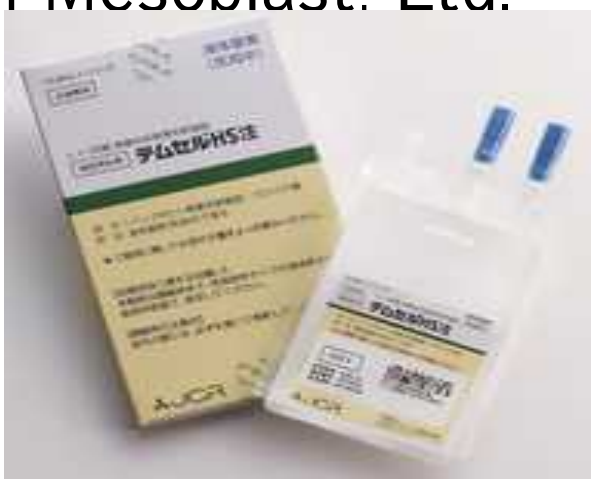
Conditional approval in Canada and New Zealand

Note: Figures quoted from the company press release docs

TEMCELL

- Target: Steroid refractory acute GVHD
  - Fatal and Rare disease (approx. 1000-2000/y)
- Product: Allogeneic MSC
- Manufacturer JCR Pharmaceuticals Co., Ltd
- Resources and technology transferred from Mesoblast. Ltd. (Osiris Therapeutics, Inc.)
  - Prochymal® (Brand Name)
    - Conditional approval in Canada and New Zealand for pediatric patients

http://www.jcrpharm.co.jp/news/20151126_3991



■Japan

- JR-031-201/202 study(Phase I/II)

  Single arm clinical trial, 14 subjects. Grade II-IV.

- JR-031-301 study (Phase II/III)

  Single arm clinical trial, 25 subjects. Grade III-IV.

■ Foreign (Prochymal®)

- 280 study

  Placebo-controlled RCT, 216 adults and 28 pediatric subjects. Grade B-D

- 275 study

  Single arm clinical trial, 75 pediatric subjects.

First approval of conditional and time-limited authorization HeartSheet

- Target:

  Serious heart failure due to Ischemic Heart Disease

  - Chronic and Poor prognosis (NYHA Class III or IV, LVEF<35%)

- Product: Autologous skeletal myoblast

- Manufacturer: Terumo Corporation

- Manufacturing

  - Biopsy from Quadriceps
  - Final product is manufactured at Cell Processing Facilities (CPF) in hospitals

HeartSheet
Manufacturing and Final Products

■ Process to Sheet Transplantation

Kit A

Container for tissues harvested

Kits for Serum separation

At Manufacturer

Kit B

Product Main Component

Frozen myoblast cells

Product Subcomponent

Kits for sheet preparation And Media

In the CPF at Hospitals

Harvest muscle tissues

Cell culture

Produce cell sheets

Myoblast Sheet

Sheet transplantation

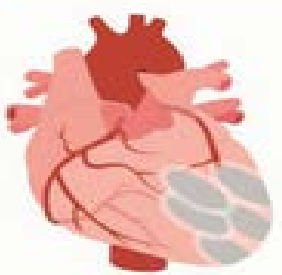


Image of a heart after sheet transplantation

Modified from

http://www.terumo.com/about/pressrelease/2015/20150902.html

Summary of Review

- Efficacy evaluation
  - LVEF (RI, CT, Echo) => surrogate endpoints
  - Comprehensive clinical evaluation

    >>Improvement of clinical symptoms
  - Survival (External control comparison)

  >> Skeletal Myoblast Sheet: All subjects survived

>> Conditional and time-limited approval

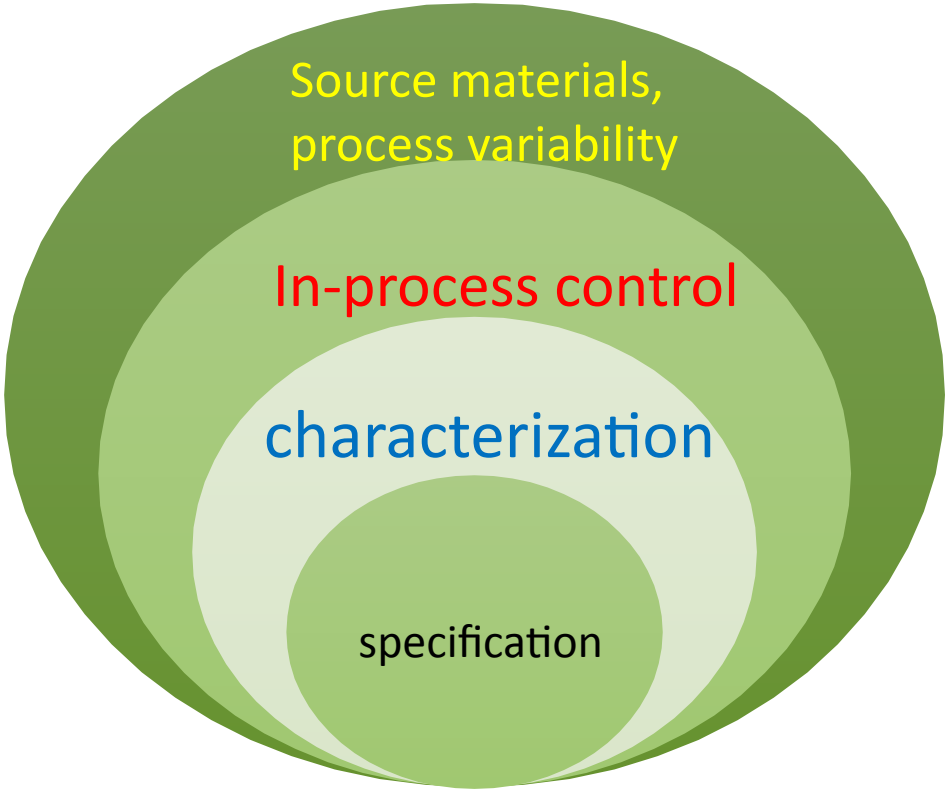
■ Post-marketing evaluation

- Concurrent external control comparison
  - Endpoint: Survival => true endpoint
  - Skeletal Myoblast Sheet: 60 subjects
  - Control: 120 subjects

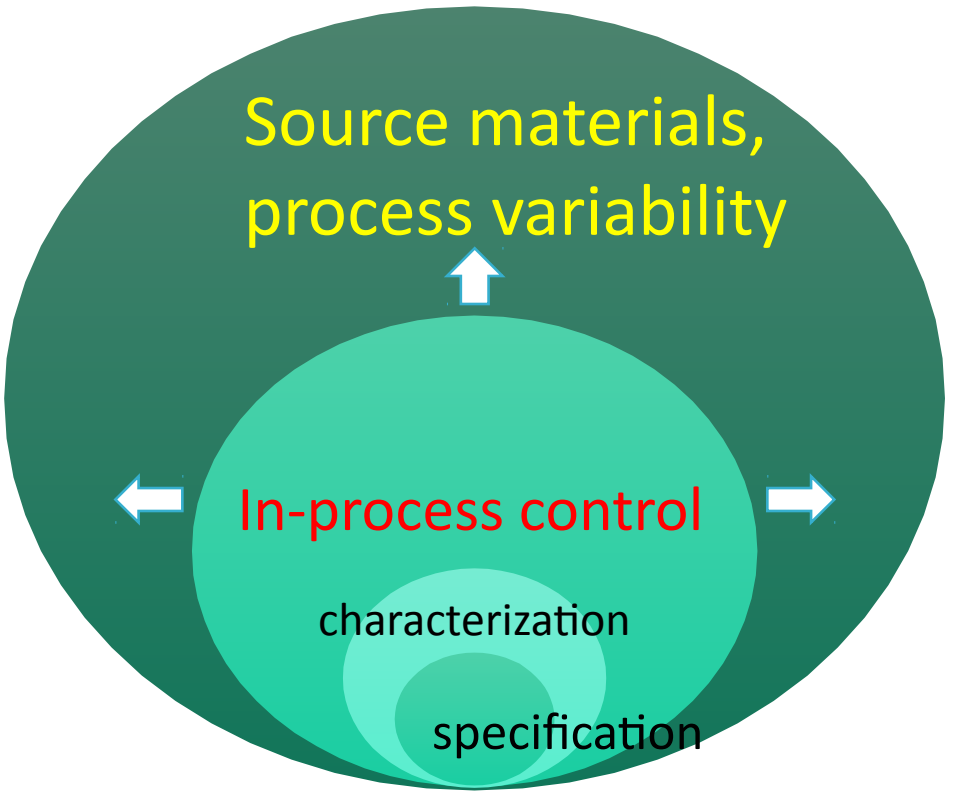
Ref.) Konishi A, Sakushima K, Isobe S, Sato D., First Approval of Regenerative Medical Products under the PMD Act in Japan. ***Cell Stem Cell***. 2016. 18(4): 434-435

Quality concept of hCTPs

Bio-pharmaceuticals

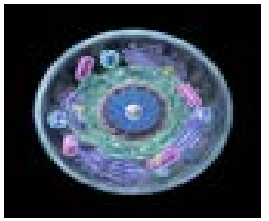


hCTPs



- Difficult to cover every aspect of quality by specification
- Limited information can be obtained from characterization and specification
- Much more rely on in-process control to control quality

Safety assessments for cellular/tissue-based products



1. Inadvertent transformation
2. Effect by active-substances produced from-cells or tissues
3. Effect on normal cells or tissue
4. Inadvertent formation of ectopic tissue
5. Undesirable immunological reactions by products
6. Tumorigenicity or Carcinogenicity
7. Safety evaluation based on guidance for products for gene therapy, when the products have transgenes.
8. General toxicity
9. Effects on vital organs
10. Safety evaluation on impurities from manufacturing processes

Pre-clinical safety evaluation

The following evaluations are needed:

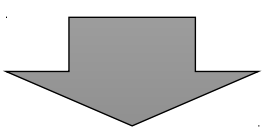
Considering product qualification;

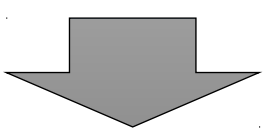
- Toxicity test/assay (including impact on life-sustaining function)
- Tumorigenicity
- Manufacturing process derived impurities

・They are subject to Clinical Trial Notification review at PMDA

General considerations for general toxicity study

Cellular/Tissue based product	*Products for gene therapy*
➢ Species differences in biological reaction ➢ Heterogenous immune responses ➢ Inappropriateness of conventional TK/ADME study	➢ Species differences in infectivity or transduction efficiency ➢ The determination of NOAEL ➢ Dose-limiting toxicity ➢ Worst-case scenario





Hazard Identification

Hazard Identification
Risk assessment

Safety and Efficacy evaluation with limited number of subjects in the trial for conditional approval

- Challenge on new designs and statistical methodologies for small population
- How to secure evidence level
  - Design : controlled? / blinded? possibility?
  - Clinical endpoint (efficacy) : clinical significance, objectiveness, surrogacy, etc.
- At least, Maximize the information from a single subject in terms of safety and efficacy.
- Post-marketing study, further confirmatory study?

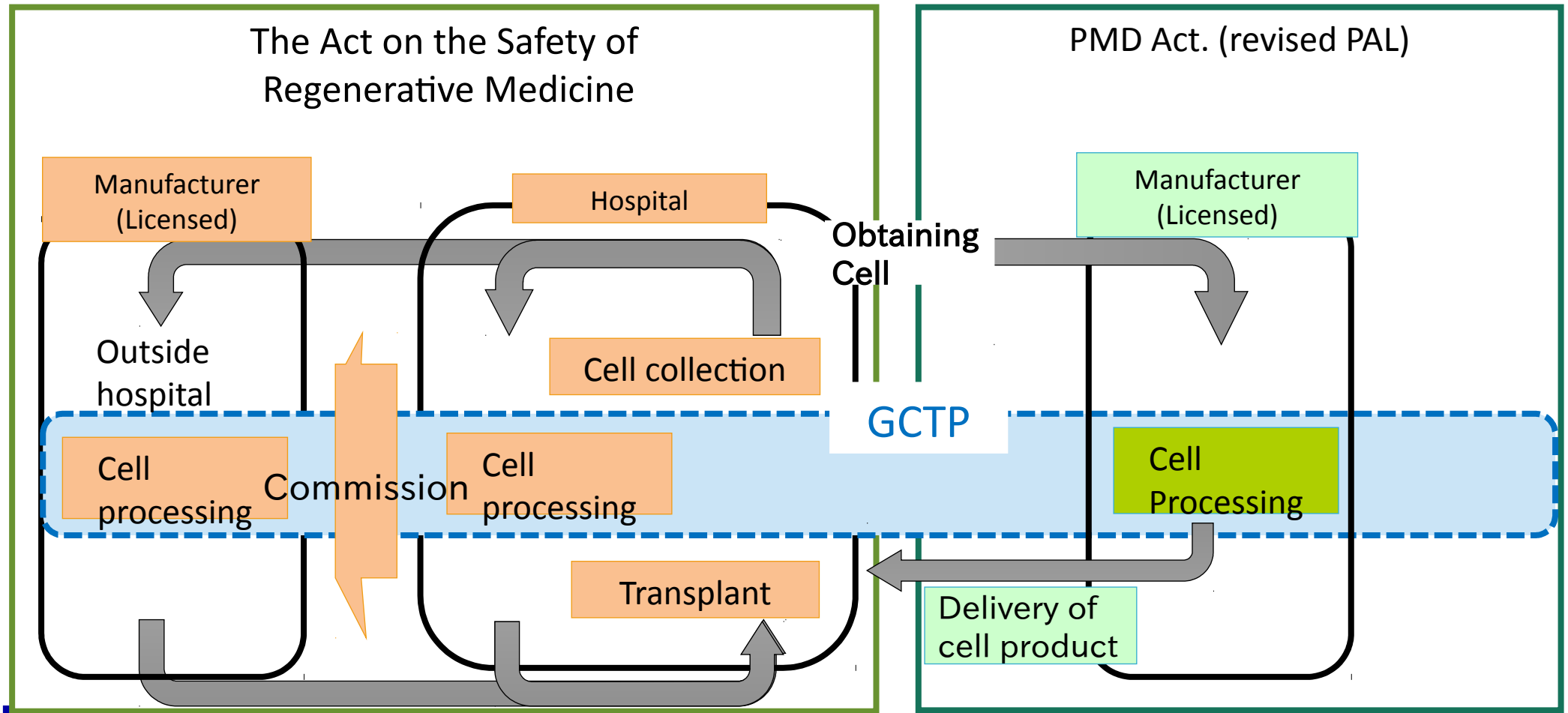
Challenges of Conditional and Time-limited Authorization

- Clinical study in post-marketing: RCT may be difficult for confirmation in some cases (single arm study with pre-agreed threshold or observational case / control study) in the postmarketing settings
  - monitoring, collection and use of real-world data, post-authorisation, as a complement to RCT data (like Adaptive pathway of EU)
- Reimbursement: Question on consistency with regulatory approval and on acceptance of clinical data for HTA payers (Japanese system is very consistent)
- CMC and quality assurance : limited qualification in early stage and quality control under GMP/GCTP (validation, scalability, comparability)

Consistent parts of the two Acts

Medical technologies using processed cells
（except clinical trials under PMD Act.）

Regenerative Medical Products



GCTP (Good gene, Cell & Tissue Manufacturing Practice)

Quality System Requirement for regenerative medical technologies / products, considering the characters of these products; such as raw materials that cannot be sterilized

- Quality Risk Management
- Manufacturing Control (Sterility assurance, Prevention of Cross-contamination..)
- Quality control (**Verification / validation**, Quality review)
- Facility requirement

It is necessary to consider whether the risk is manageable,
- not only from the facility point of view,
- but from the effects of the manufacturing operation, such as the evaluation of performance.

ICH Consideration Papers on Gene Therapy Products

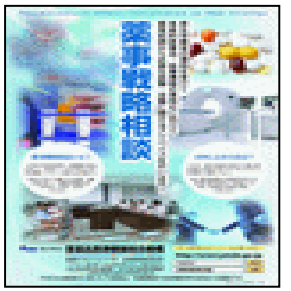
- ICH Considerations General Principles to Address Virus and Vector Shedding (June 2009)
- ICH Considerations Oncolytic Viruses (November 2008)
- ICH Considerations General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (October 2006)

These points to consider will be made public as a notification from MHLW. (in Japanese)

Facilitate Development

Scientific Advice Scheme

Pharmaceutical Affairs Consultation on R&D Strategy for scientific advice



Basic Research

Pharmaceuticals and Medical Devices candidates

Strategic Consultation

Quality Study

Non-Clinical Study

Clinical Trial

(Up to POC studies)

Practical Use

Innovative Products

* Further studies are handled by the Regular Consultation

Consultation on quality and battery of pre-clinical, including examining tumorigenicity, biological ingredient safety

Consultation on endpoints or sample size of early clinical trial

Flow of Strategy Consultation

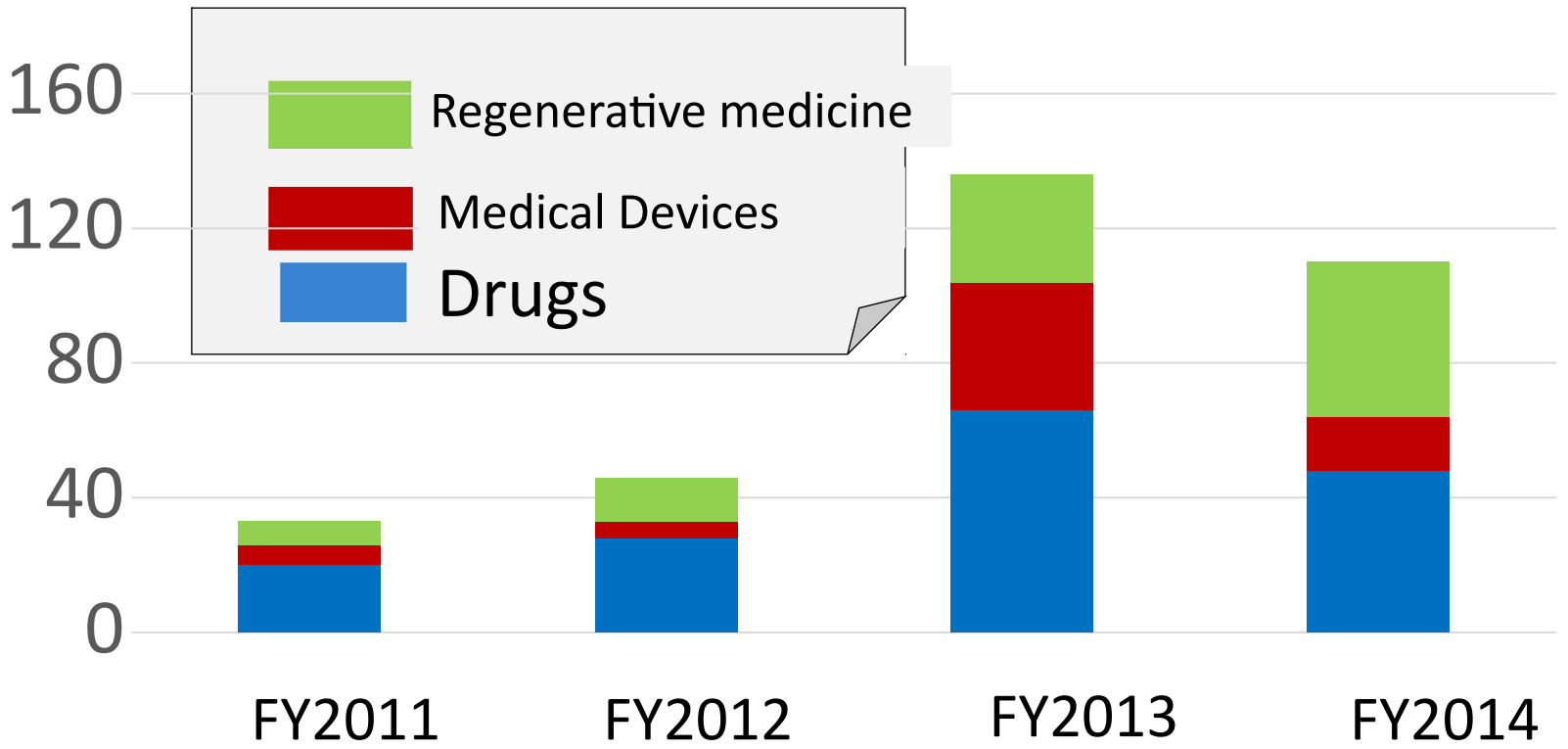
Introductory Consultation	Pre-Consultation	Face-to-Face Consultation
(1,149)	(1,490)	(466)

(7/1/2011 – 3/31/2016)

Pharmaceutical Affairs Consultation on R&D Strategy

（category）

N of consultation



66 consultations come under regenerative category in FY2015

PMDA for the world

-To create society to receive the essential forefront medicines-

Swift approvals of innovative products

Convey Japanese technology to the world

Contribute to the world's medicine

Cooperate with all agencies in the world

Review

Full measures by use and application of medical information

Swift relief for occurred health damage

Japanese citizens

Safety

Relief

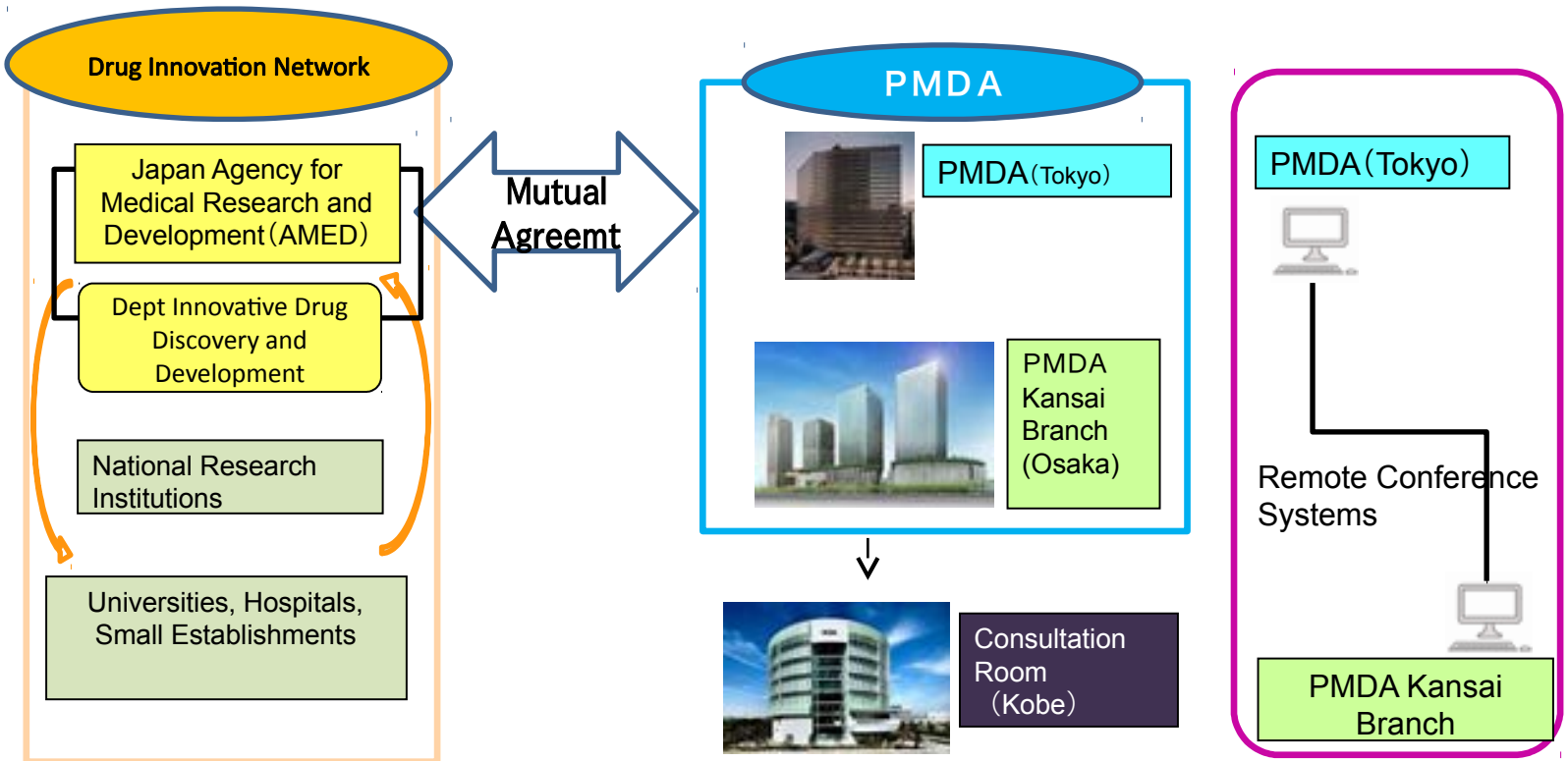
Regulatory Science

PMDA Kansai Branch

(back ground) Kansai area is very active in medical research including regenerative medicine.
【Location】 Grand Front Osaka Building in Umeda, Osaka (5 min walk from Osaka station)

【Opened】 October 1, 2013
【Operations】 Pharmaceutical Affairs Consultation (pre-meeting and advisory meeting), GMP/GCTP/QMS inspection

Supported by MHLW, MEXT, and METI



Starting June 15, all the consultations can take place in Kansai Branch via Remote Conference System

Thank You for your attention!

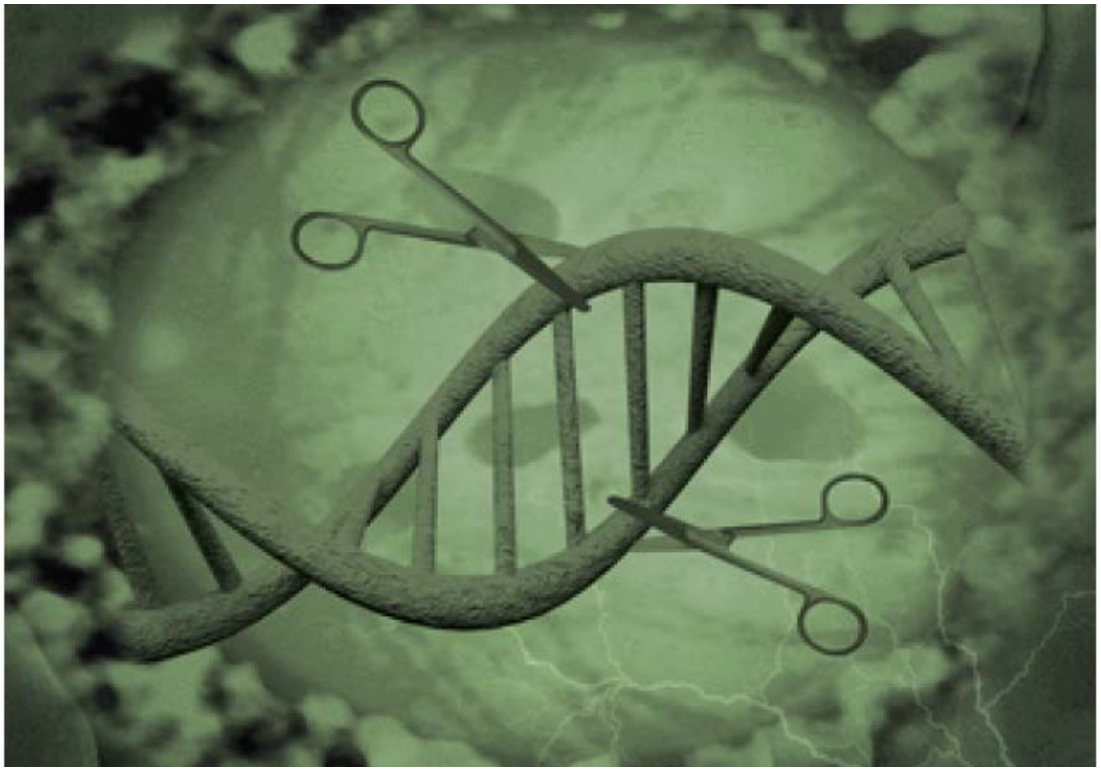
Thanks to my colleagues of Office of Cellular and Tissue-based Products

Literature available in English:

(1) Hara A. Sato D. Sahara Y. New Governmental Regulatory System for Stem Cell–Based Therapies in Japan. ***Therapeutic Innovation & Regulatory Science***. 2014; 48(6): 681-688.

(2) Konomi K. Tobita M. Kimura K. Sato D. New Japanese Initiatives on Stem Cell Therapies. ***Cell Stem Cell.*** 2015; 16 (4): 350-352.

Programmable nucleases and next generation gene therapy
(유전자가위 기술과 미래 질병 치료기술)

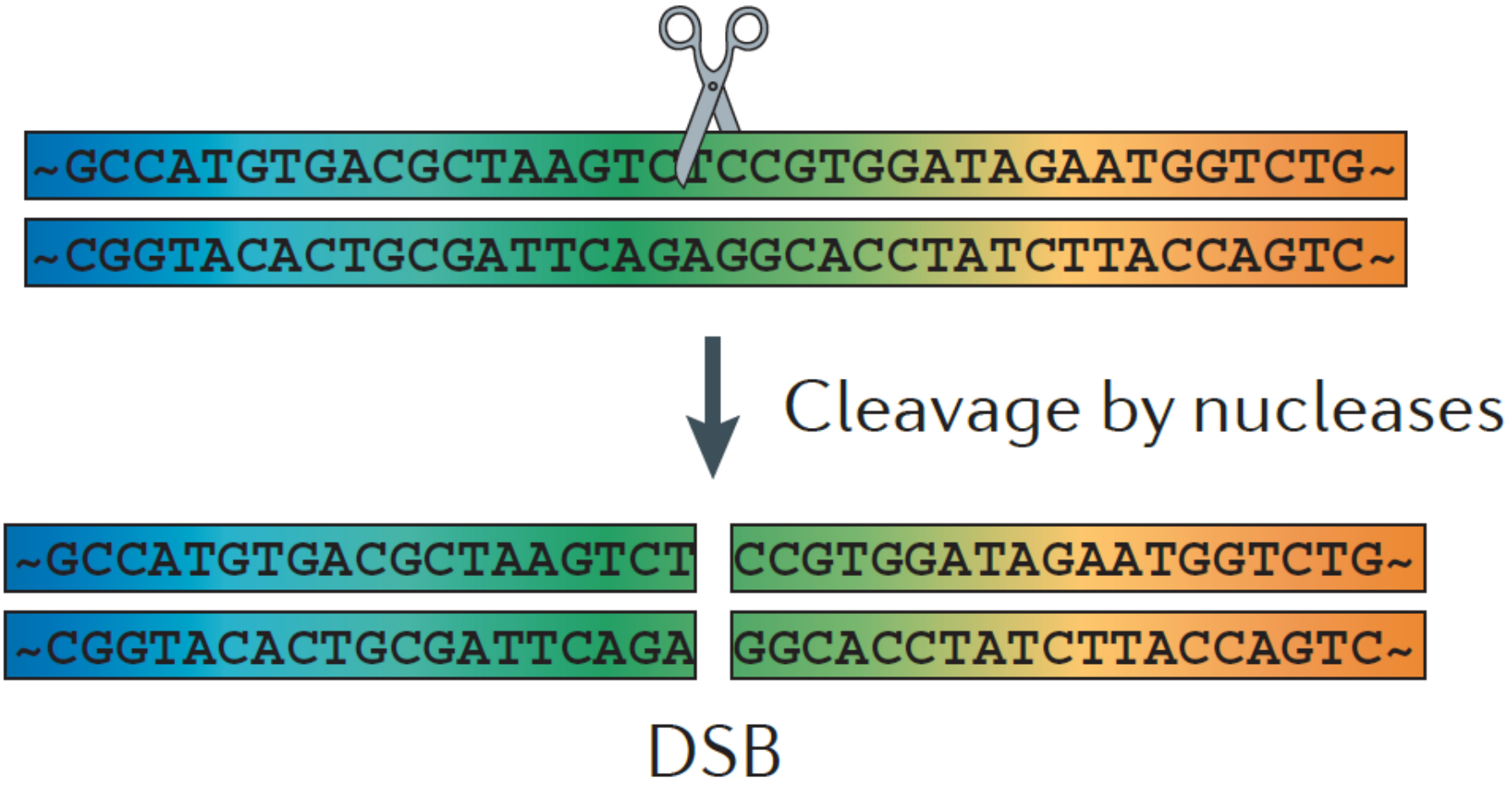


연세대학교 약리학교실
DEPARTMENT OF PHARMACOLOGY
YONSEI UNIVERSITY COLLEGE OF MEDICINE

Hyongbum Kim, M.D., Ph.D.

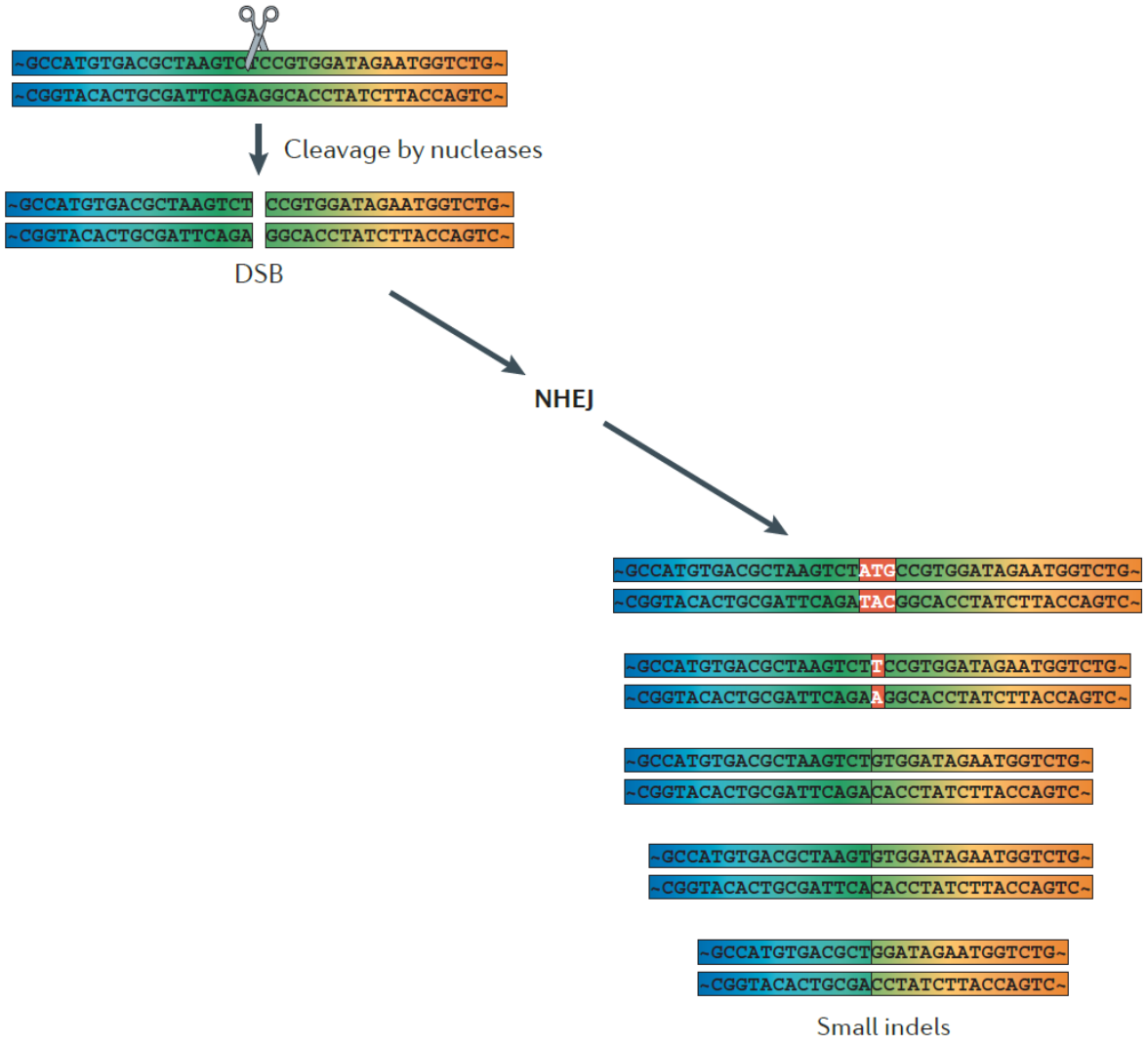
June 28, 2016

What do programmable nucleases do?



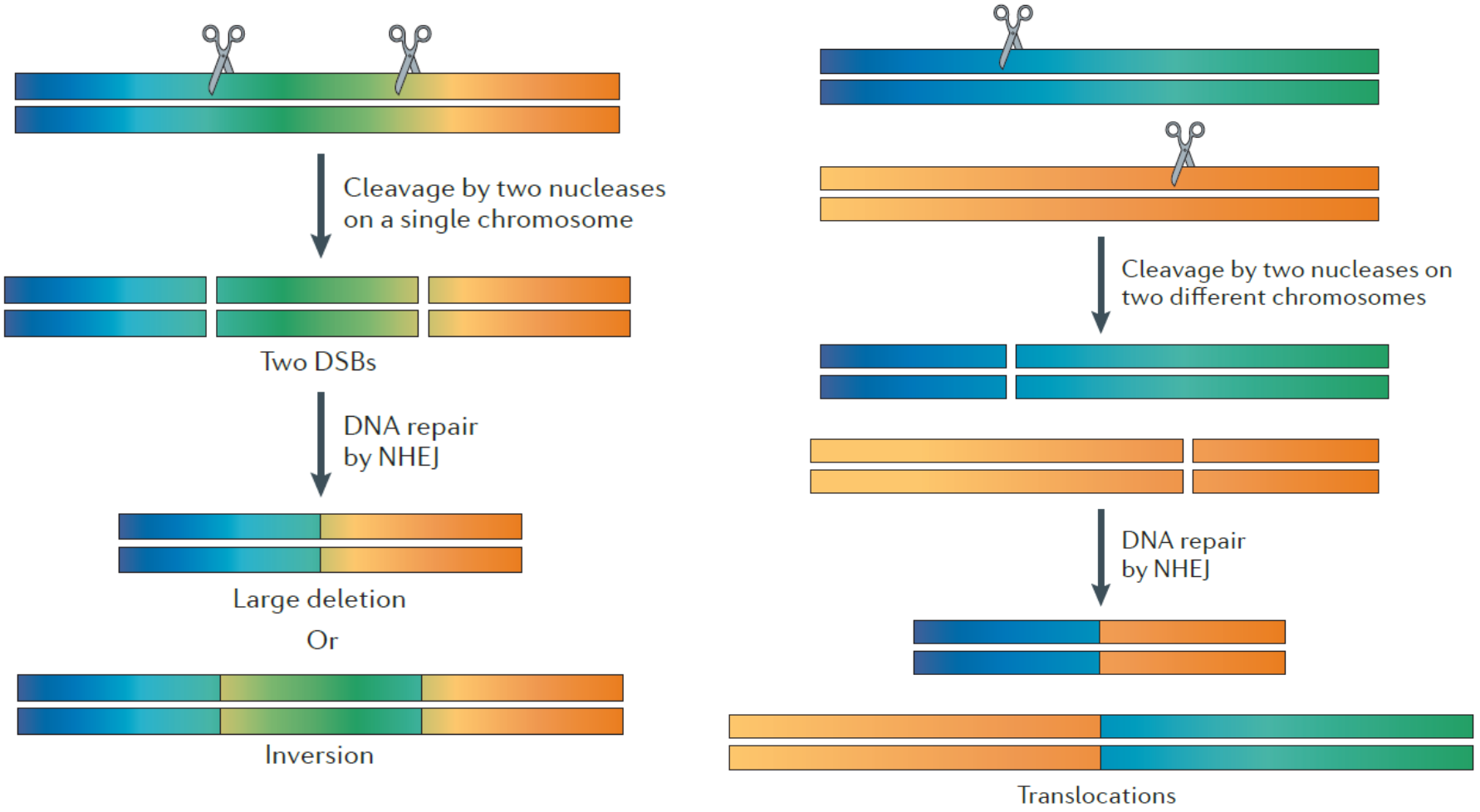
Kim H and Kim JS, Nat. Rev. Genet., 2014

Genome Engineering by programmable nucleases



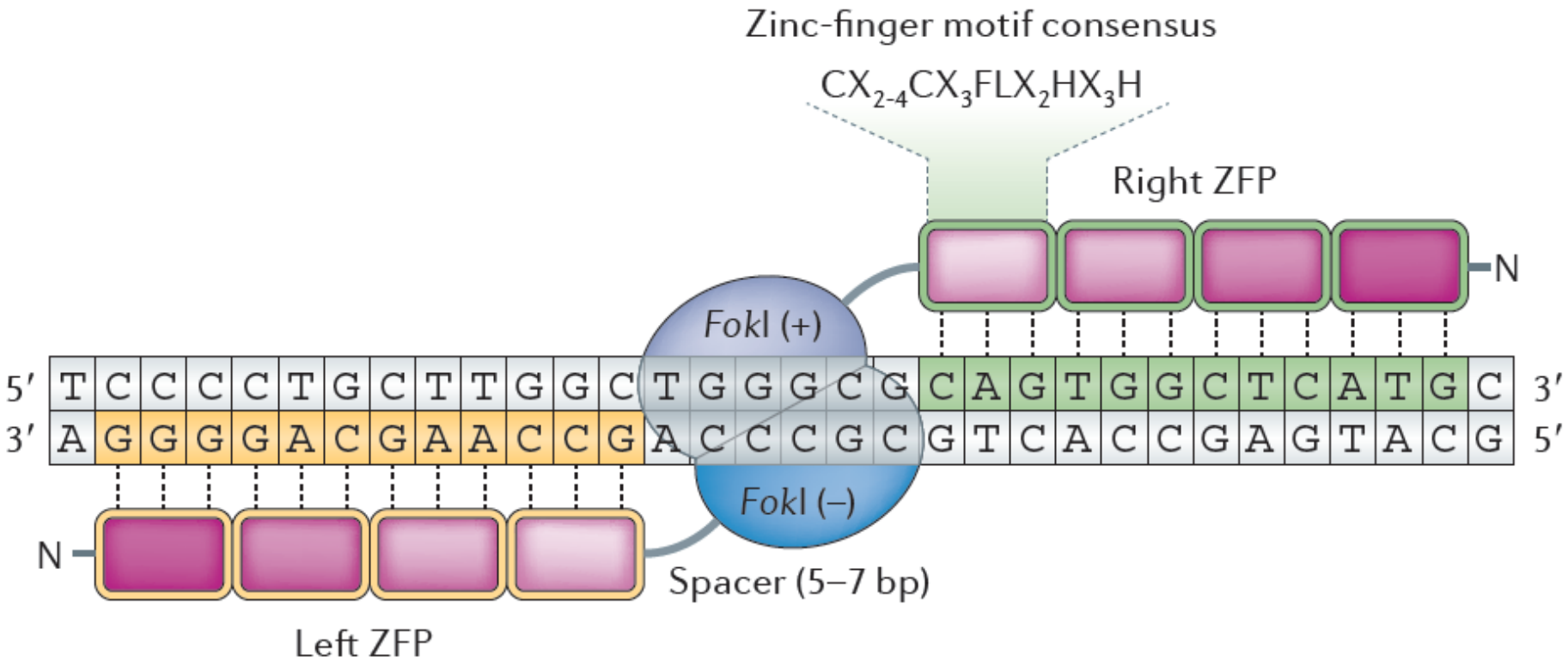
Kim H and Kim JS, Nat. Rev. Genet., 2014

Chromosomal rearrangements by programmable nucleases



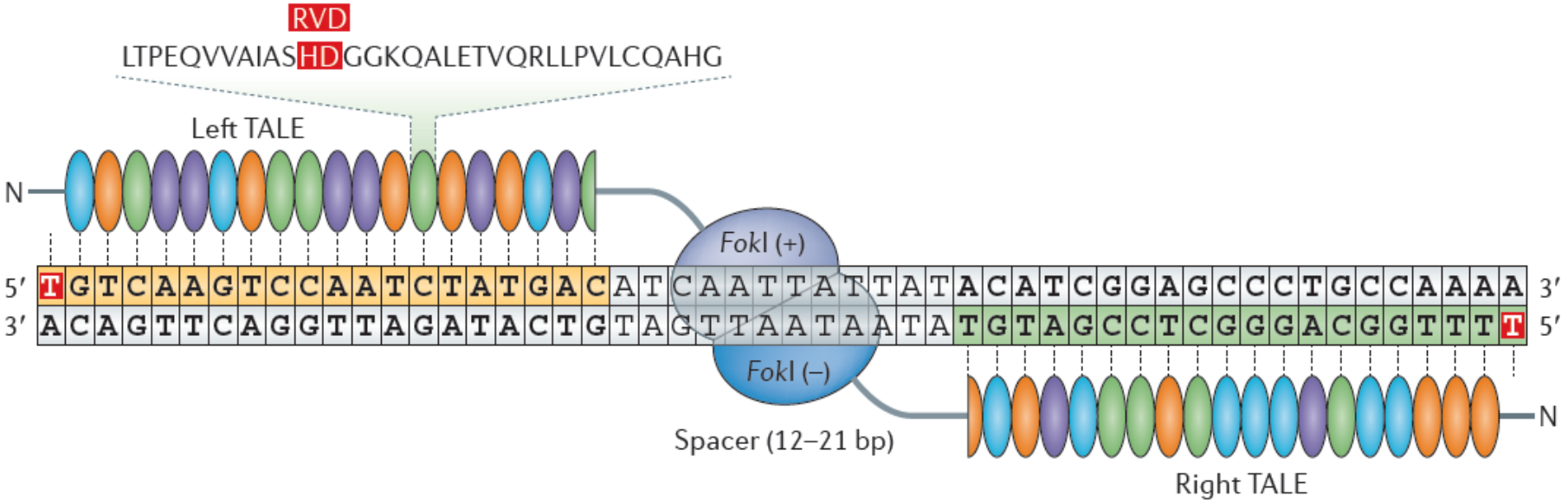
Kim H and Kim JS, Nat. Rev. Genet., 2014

Zinc finger nucleases



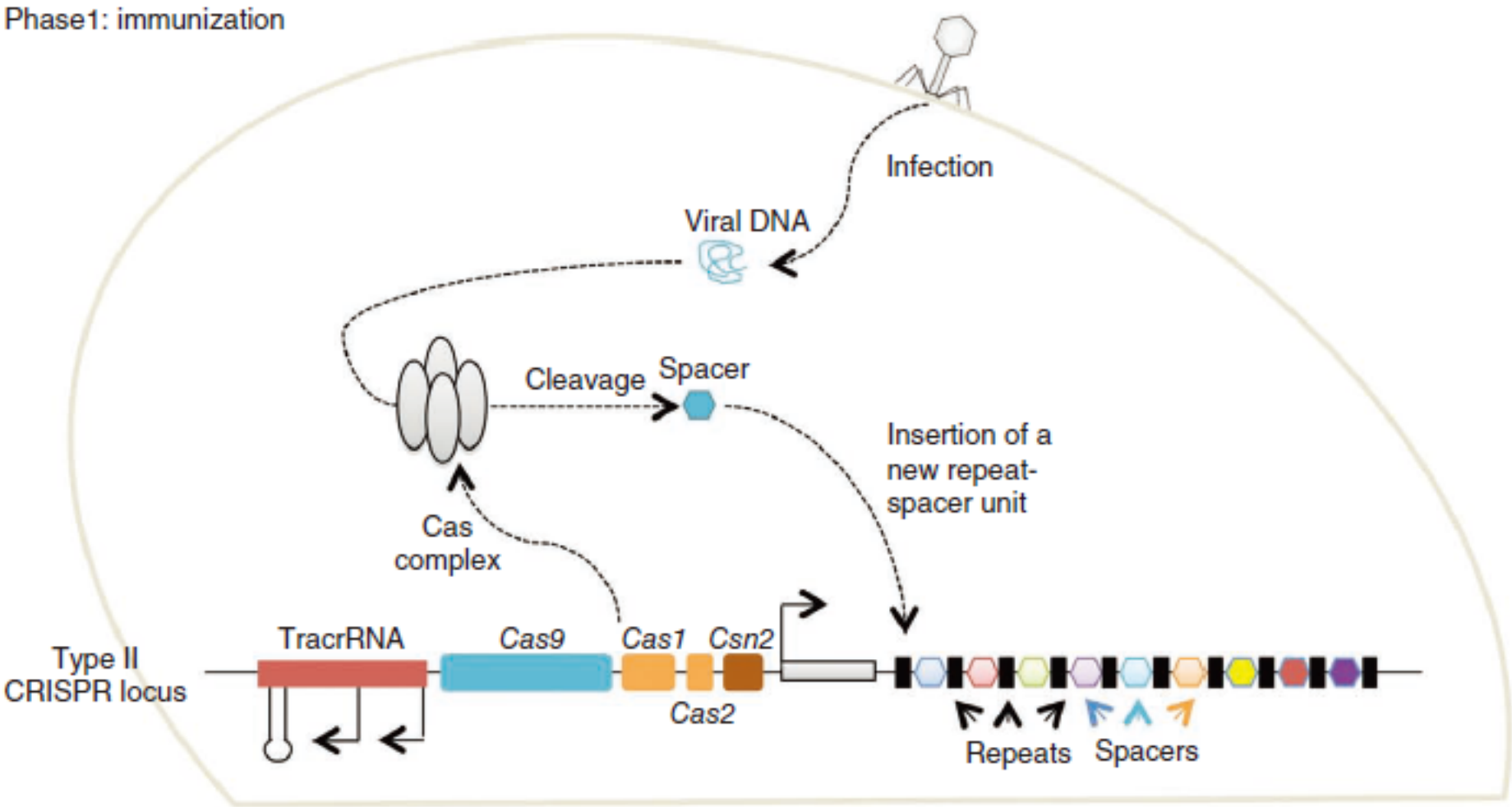
Kim H and Kim JS, Nat. Rev. Genet., 2014

Transcription activator-like effector nucleases



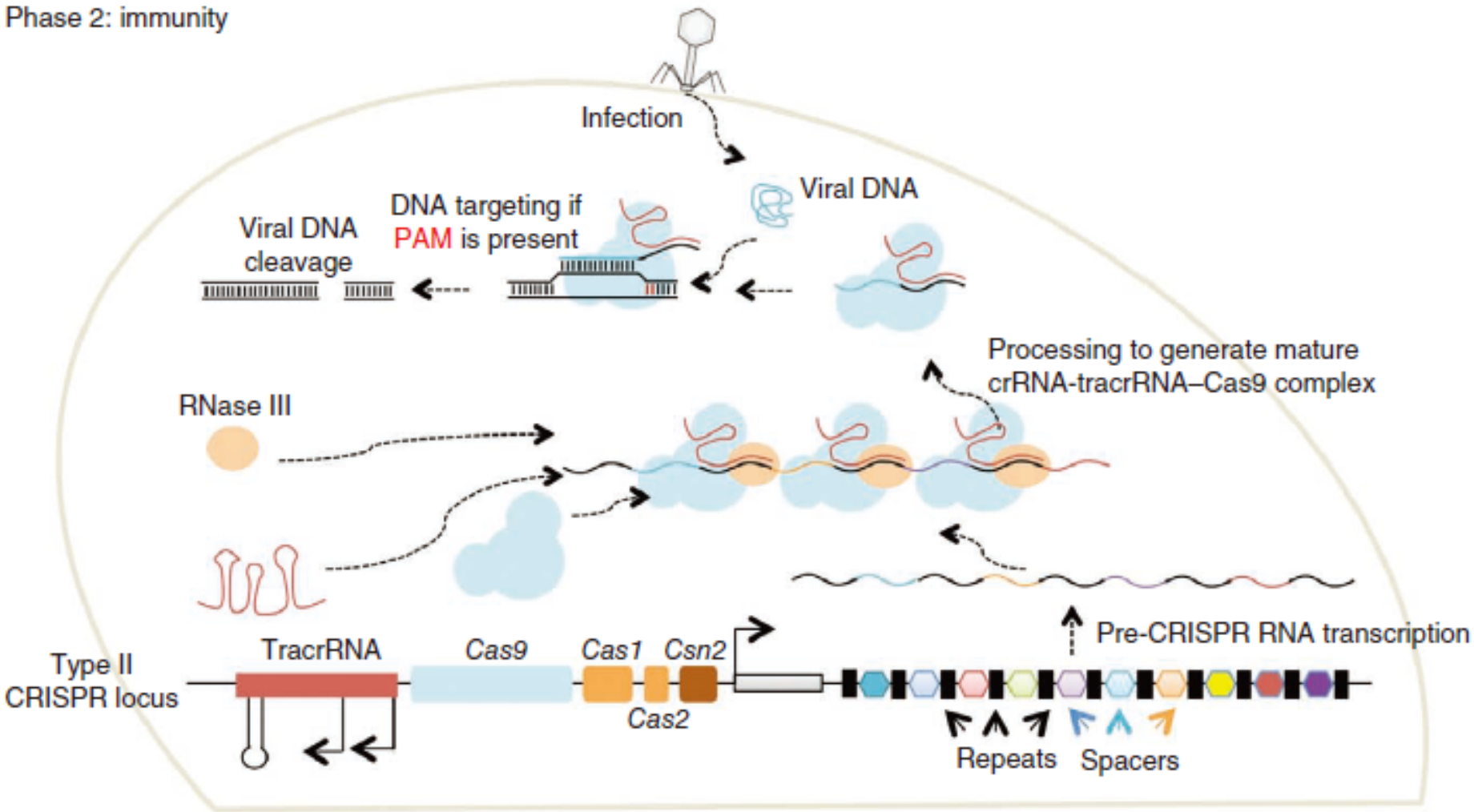
Kim H and Kim JS, Nat. Rev. Genet., 2014

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas)9 system



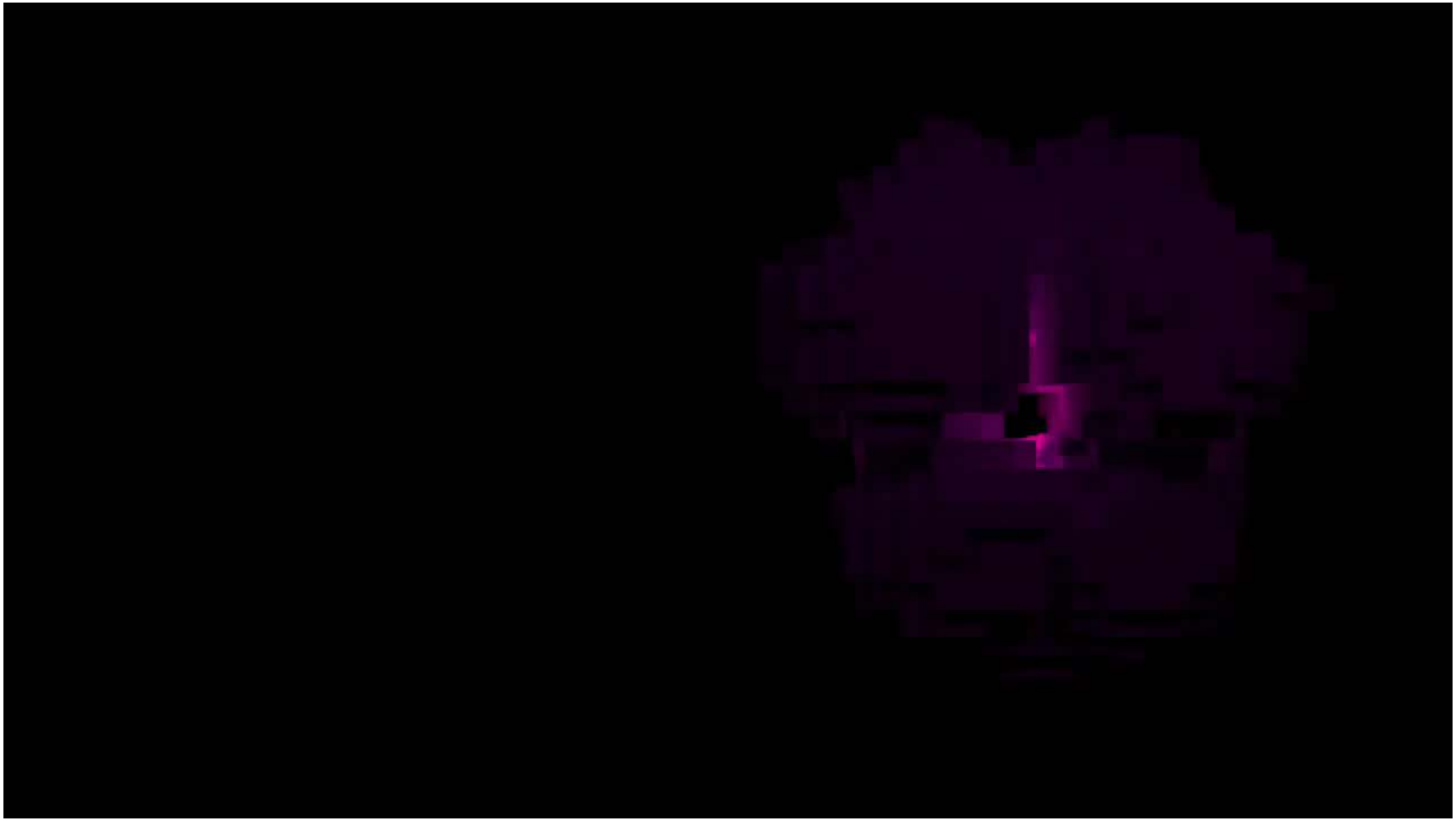
Mali et al. 2013 Nat. Methods

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated (Cas)9 system



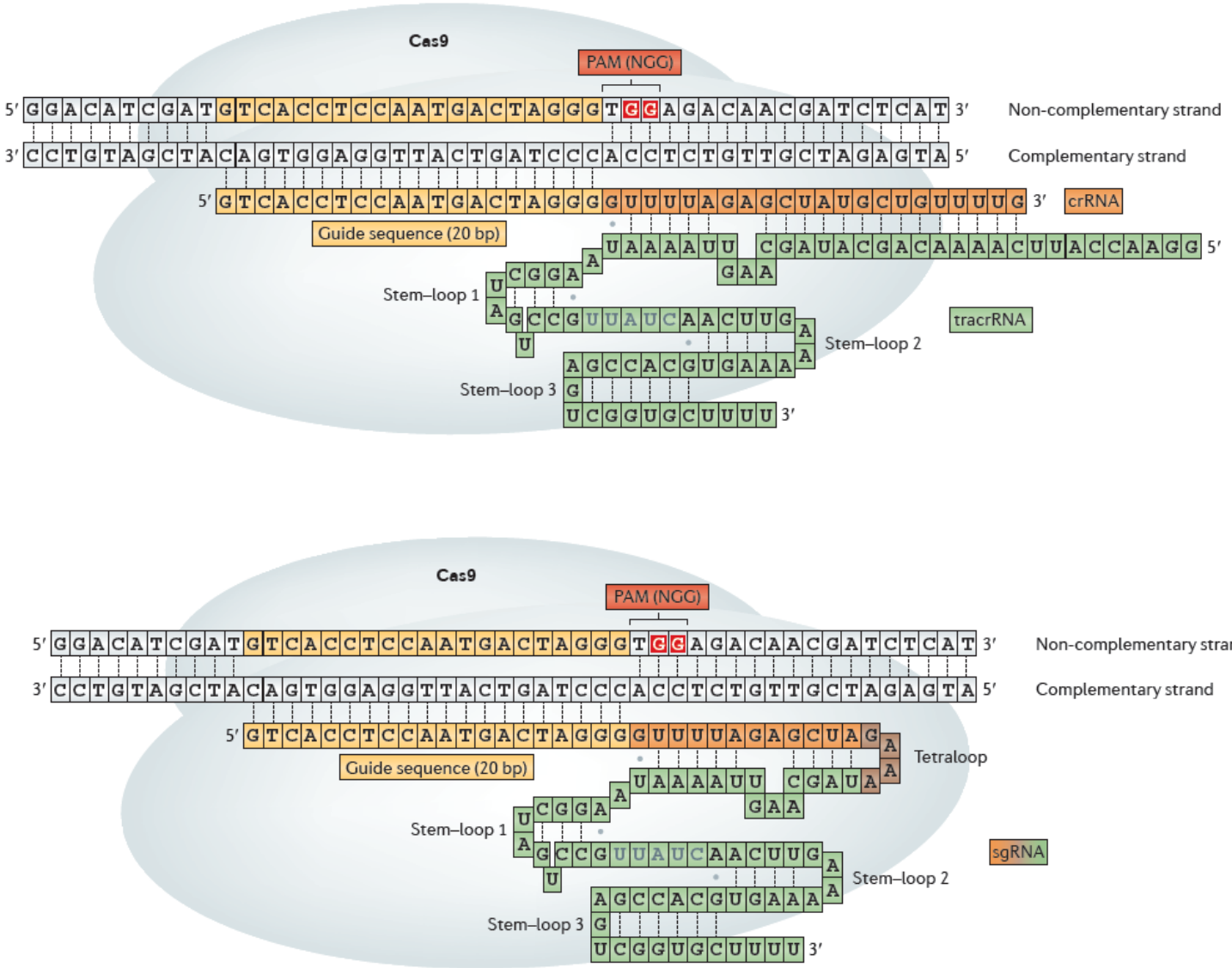
Mali et al. 2013 Nat. Methods

Cas9-mediated DSB generation in viral genomes

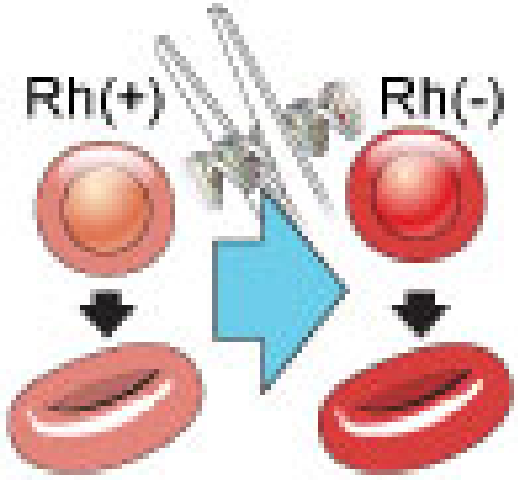


https://www.youtube.com/watch?v=M739wgbcKuA

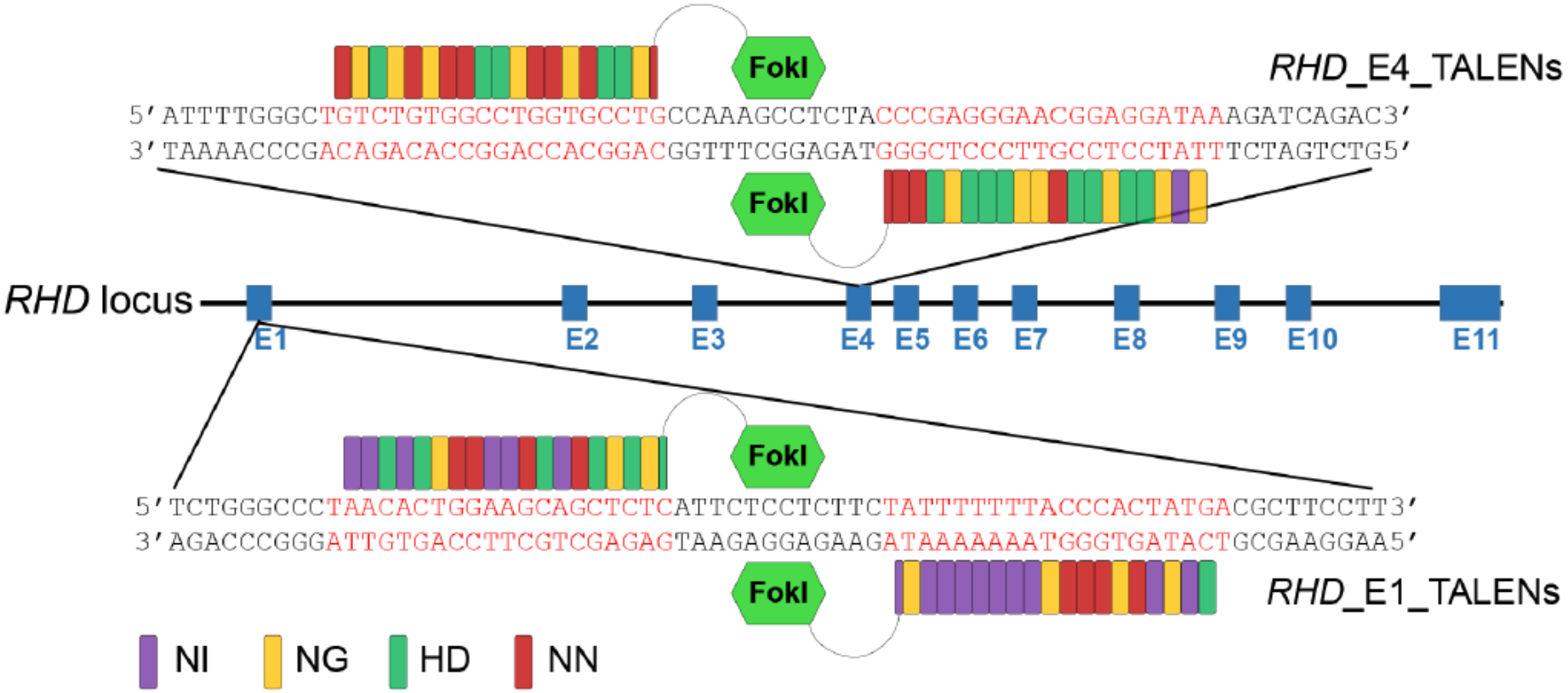
RNA-guided engineered nucleases



Kim H and Kim JS, Nat. Rev. Genet., 2014

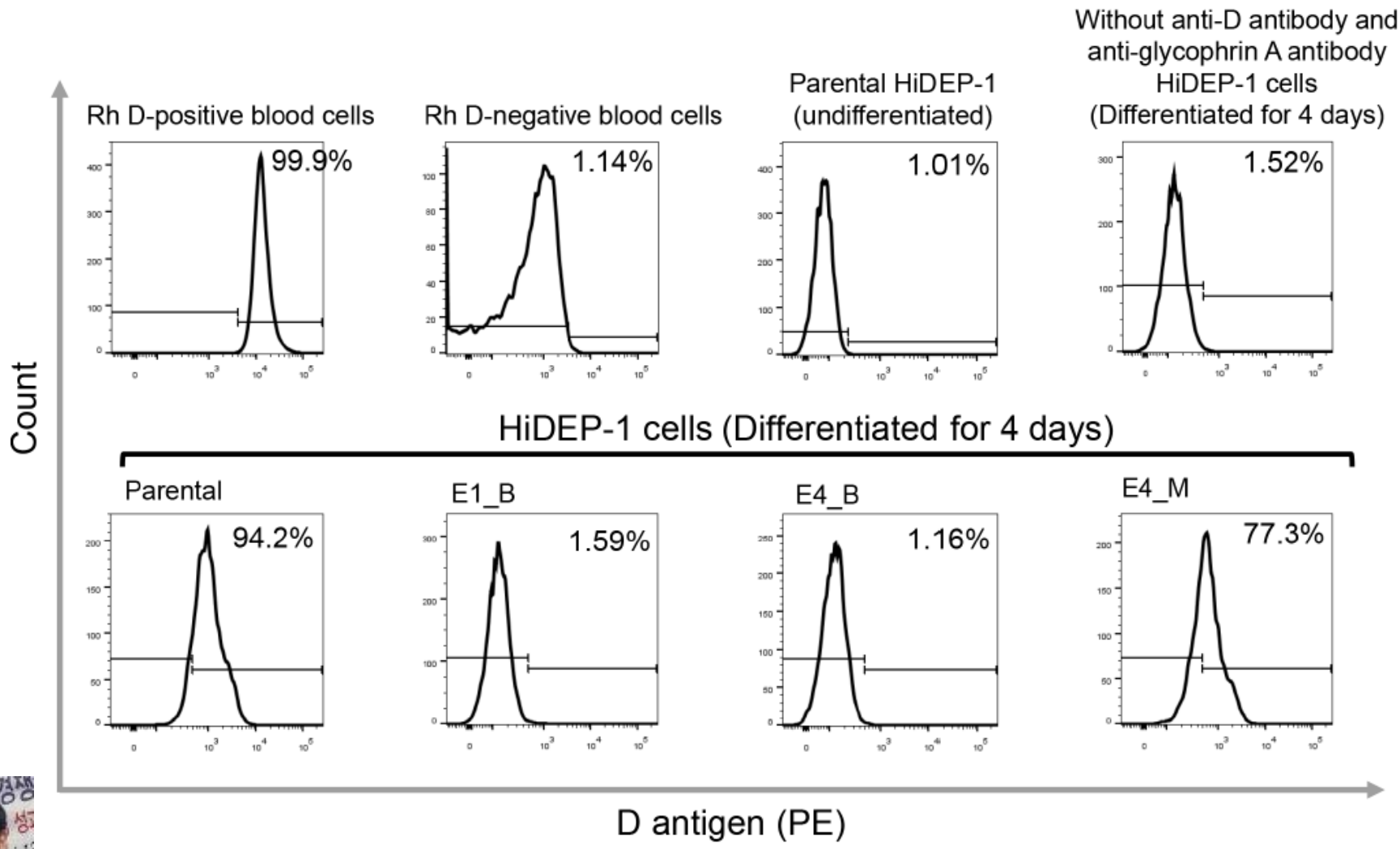

Rh(+)
Rh(-)

RHD-targeting TALENs



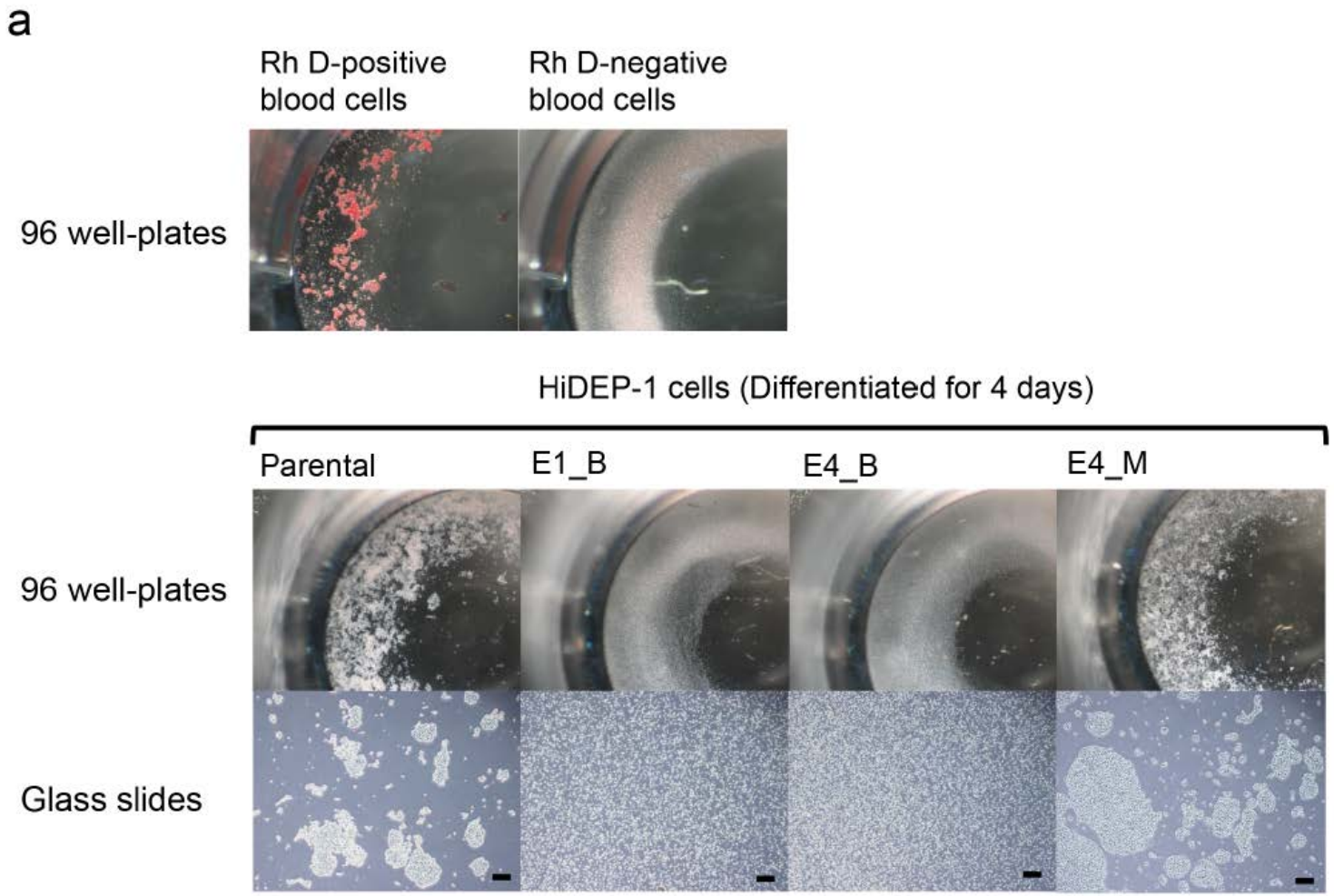
Kim et al., Nat. Commun., 2015

TALEN-induced RHD knockout in erythroblasts



Kim et al., Nat. Commun., 2015

Conversion of Rh D positive erythroblasts into Rh D negative ones

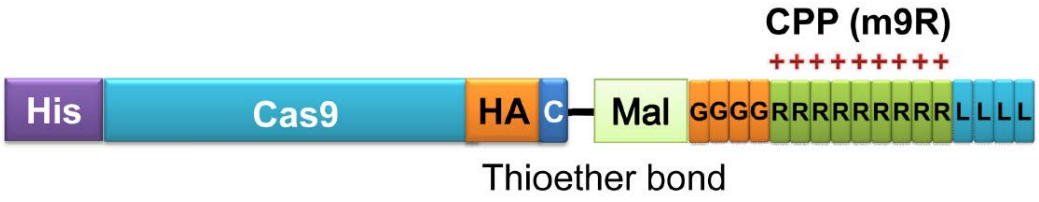


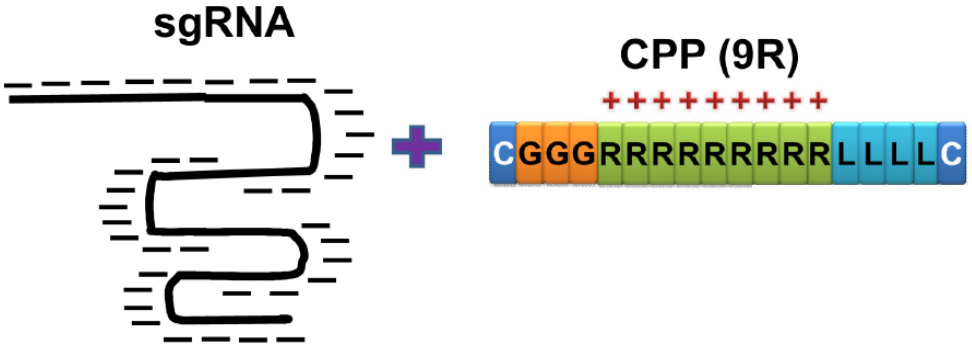
Kim et al., Nat. Commun., 2015

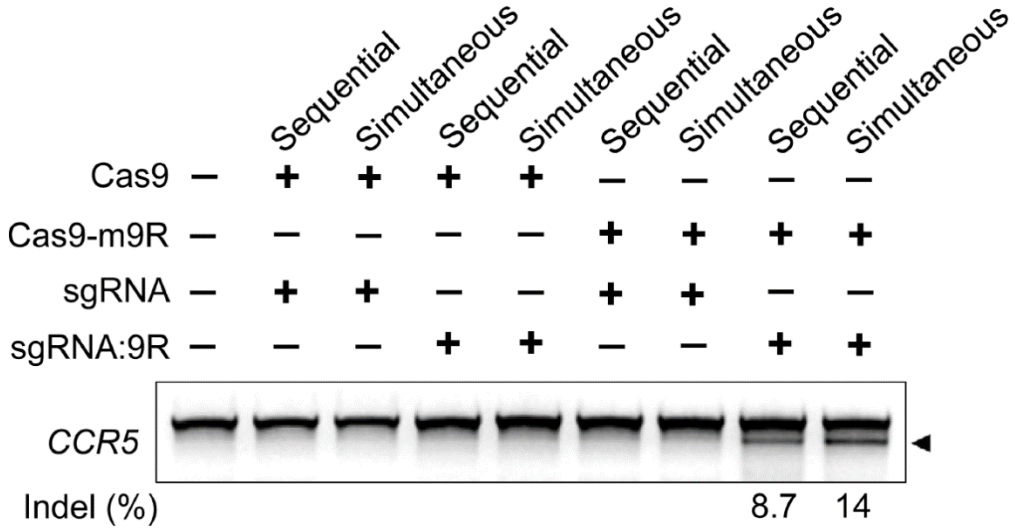
Potential problems of plasmid-mediated delivery

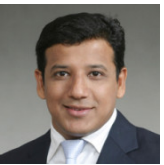
- Unwanted immune responses caused by bacterial sequences
- Uncontrolled integration of the plasmid DNA into the host genome

Gene disruption through CPP-mediated delivery of Cas9 protein and guide RNA





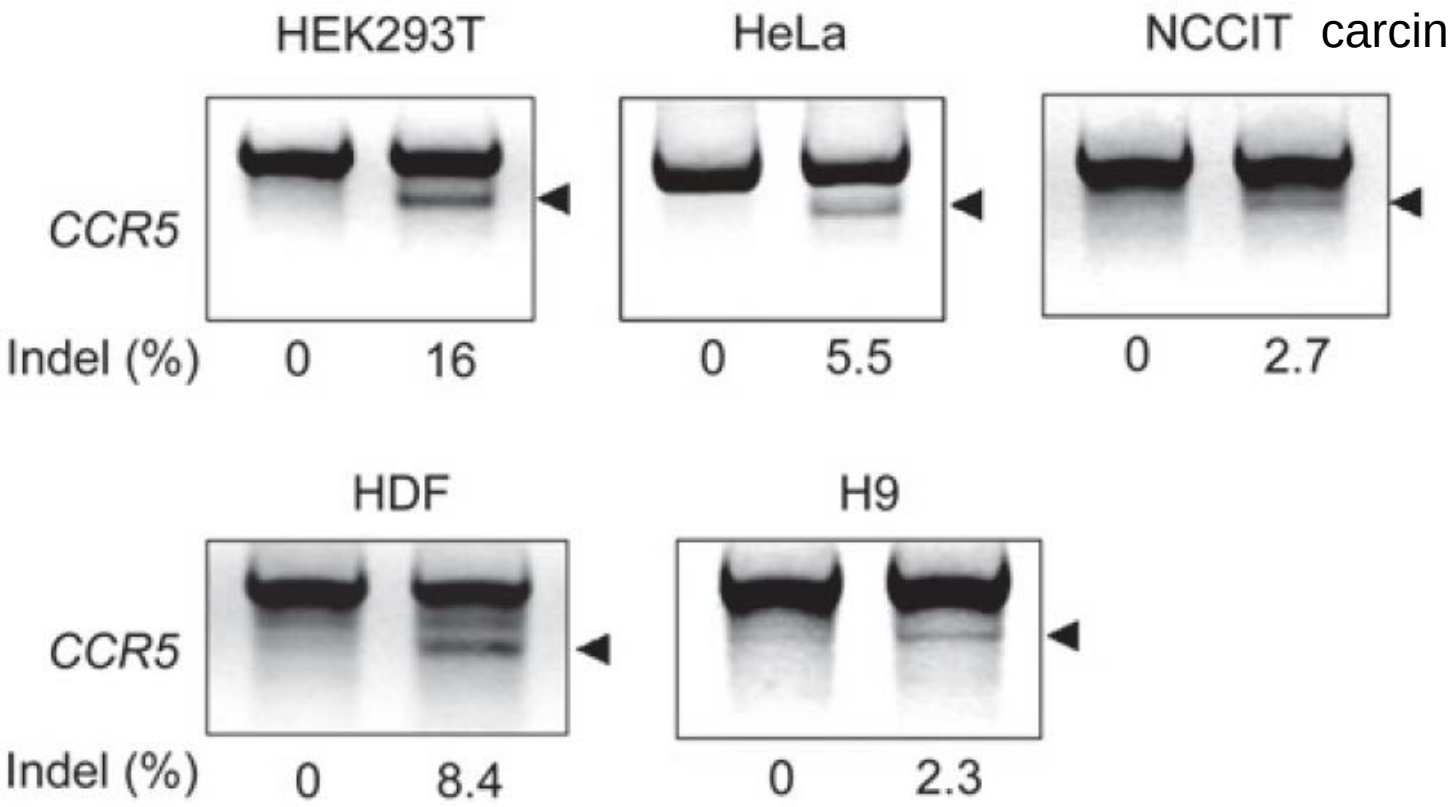


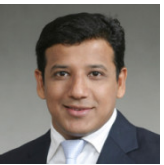


Ramakrishna et al., Genome Res., 2014

Gene disruption through CPP-mediated delivery of Cas9 protein and guide RNA in several cell lines

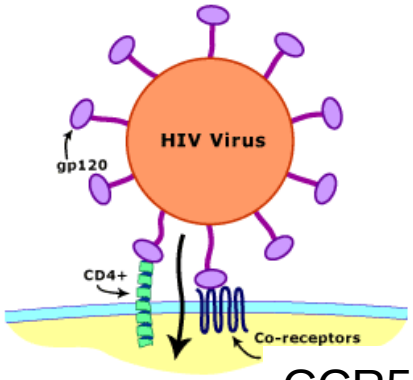
(human embryonal carcinoma cell line)





Ramakrishna et al., Genome Res., 2014

Treatment of HIV infection using ZFNs



CCR5

The NEW ENGLAND JOURNAL of MEDICINE

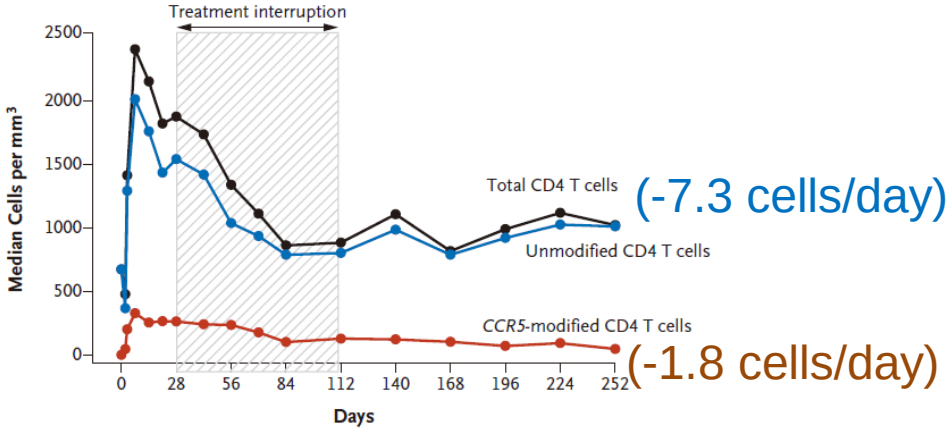
ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

Timothy Brown

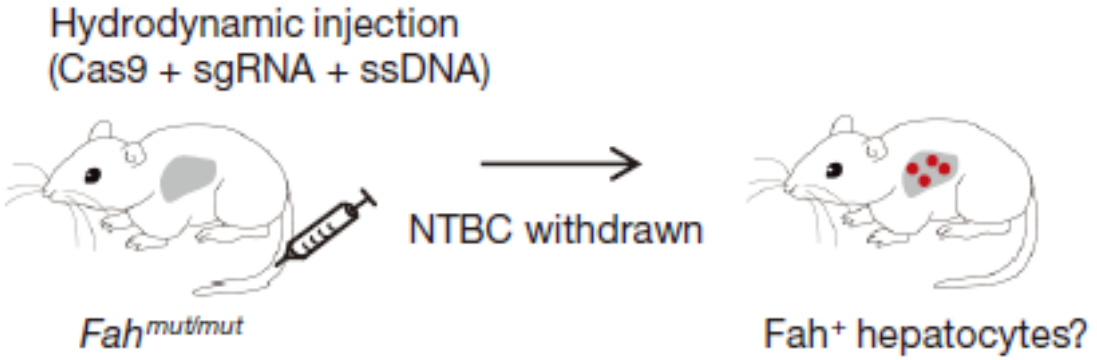
HIV infection +
AML (leukemia)



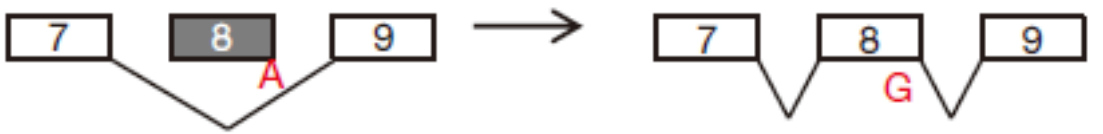
Tebas et al., N. Eng. J. Med., 2014

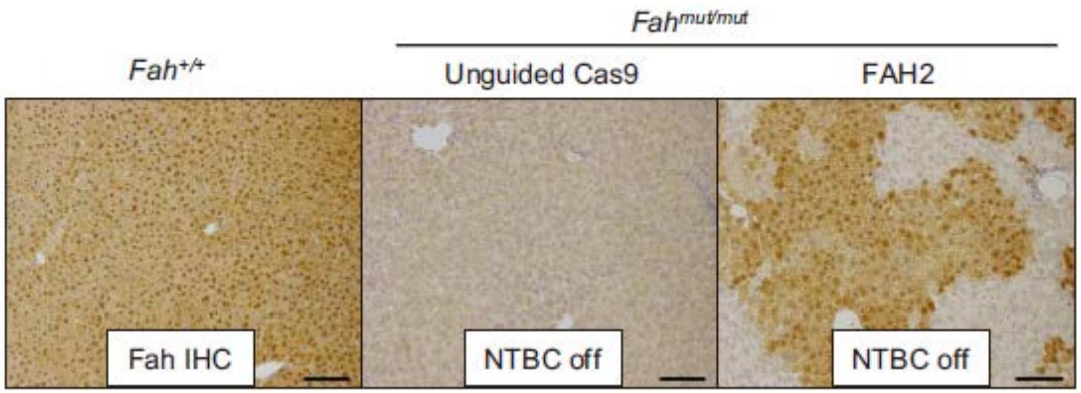
In vivo genome editing using RGENs-Hereditary tyrosinemia

Hereditary tyrosinemia type I (mutation of fumarylacetoacetate hydrolase)



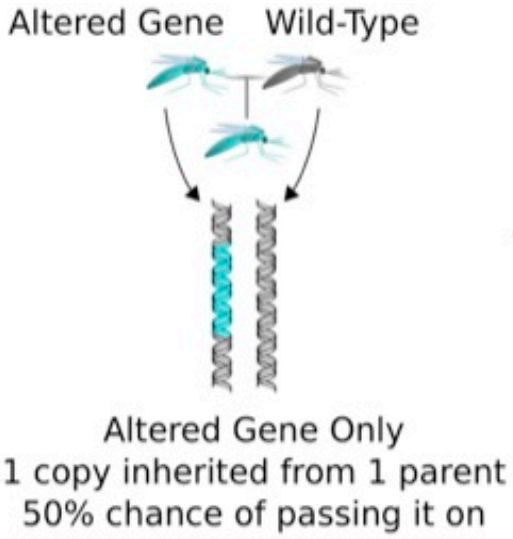
5′…CCTCATGAACGACTGGAGCGgtaatgcctggtgg…3′ ssDNA
5′…CCTCATGAACGACTGGAGCAgtaatgcctggtgg…3′ genomic

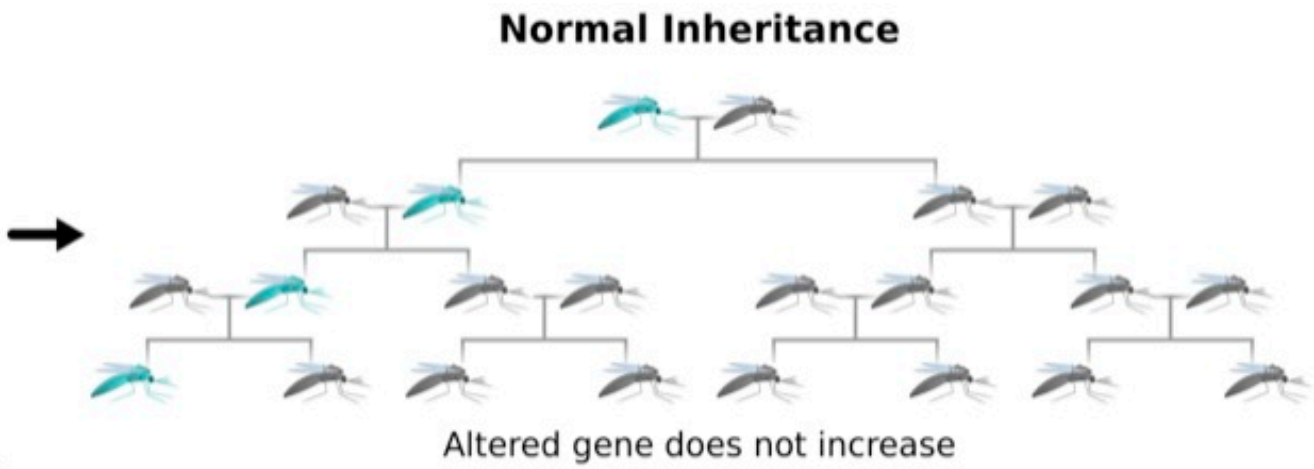


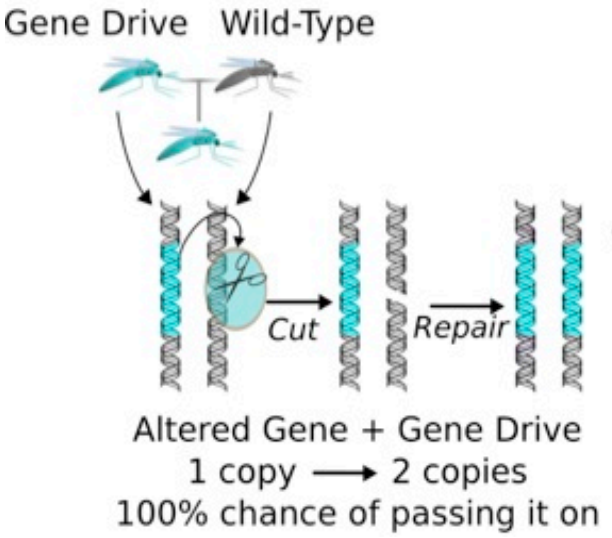


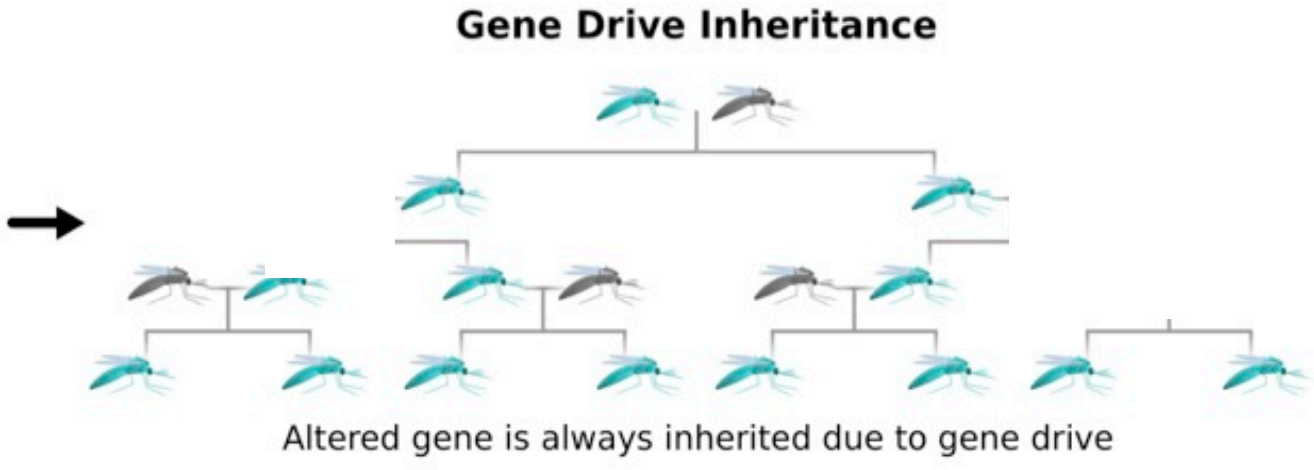
Yin et al., Nat. Biotech., 2014

Gene drive

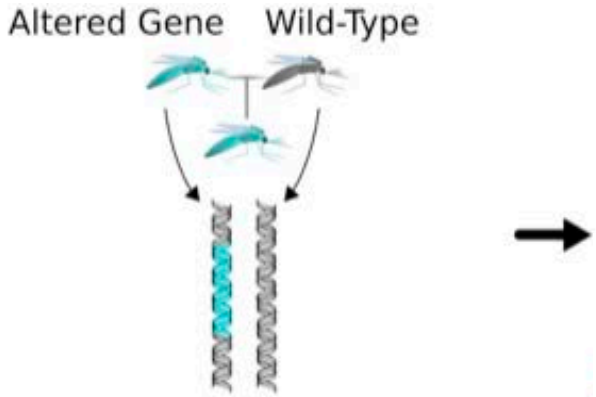

Altered Gene
Wild-Type
Altered Gene Only
1 copy inherited from 1 parent
50% chance of passing it on


Normal Inheritance
Altered gene does not increase

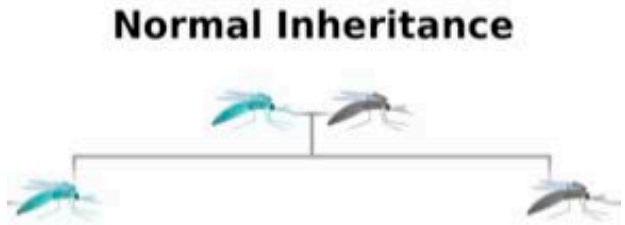

Gene Drive
Wild-Type
Cut
Repair
Altered Gene + Gene Drive
1 copy ⟶ 2 copies
100% chance of passing it on


Gene Drive Inheritance
Altered gene is always inherited due to gene drive

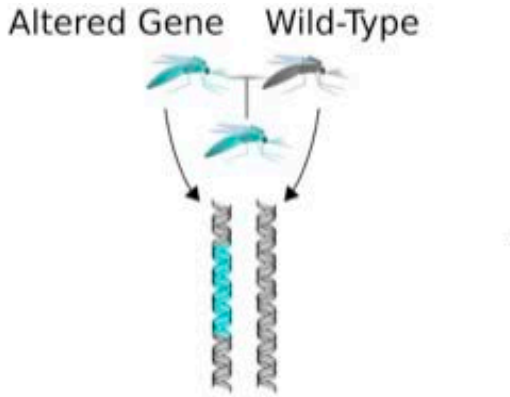
Gene drive



Altered Gene Only
1 copy inherited from 1 parent
50% chance of passing it on



Gene drive



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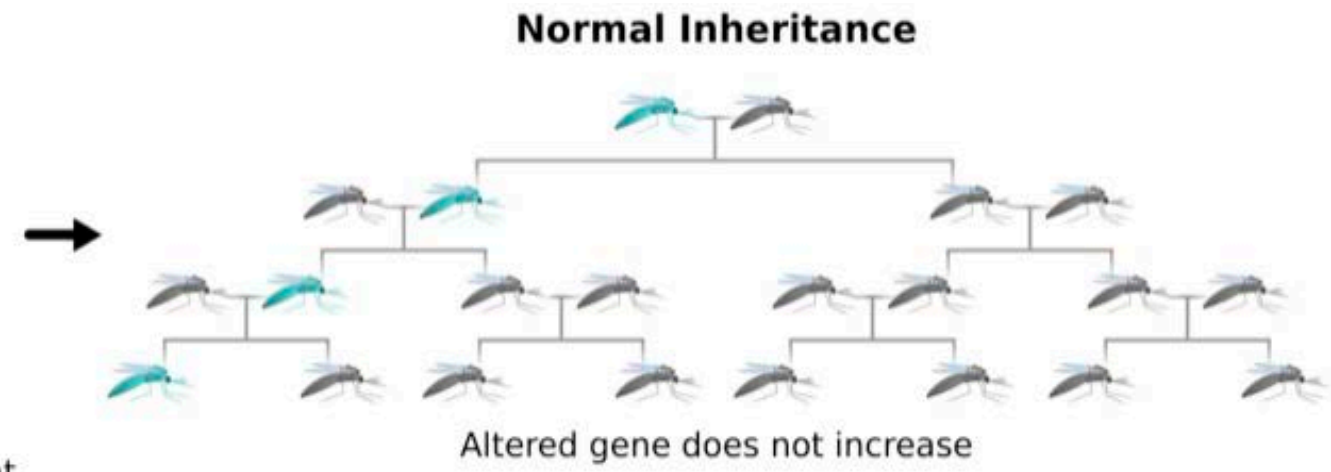
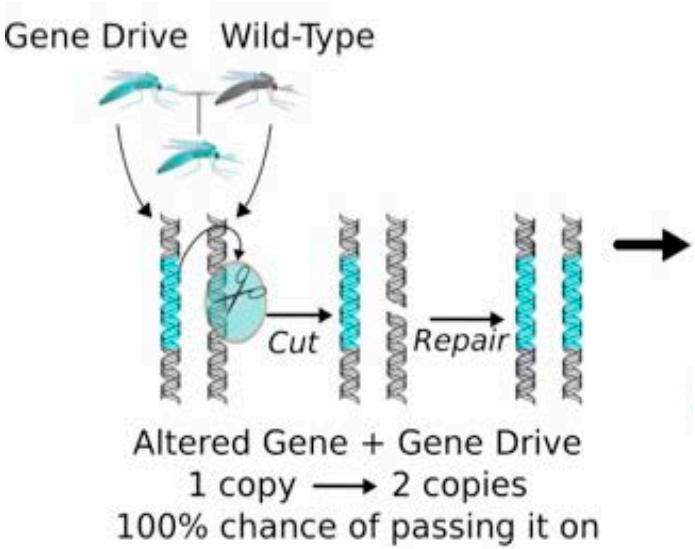


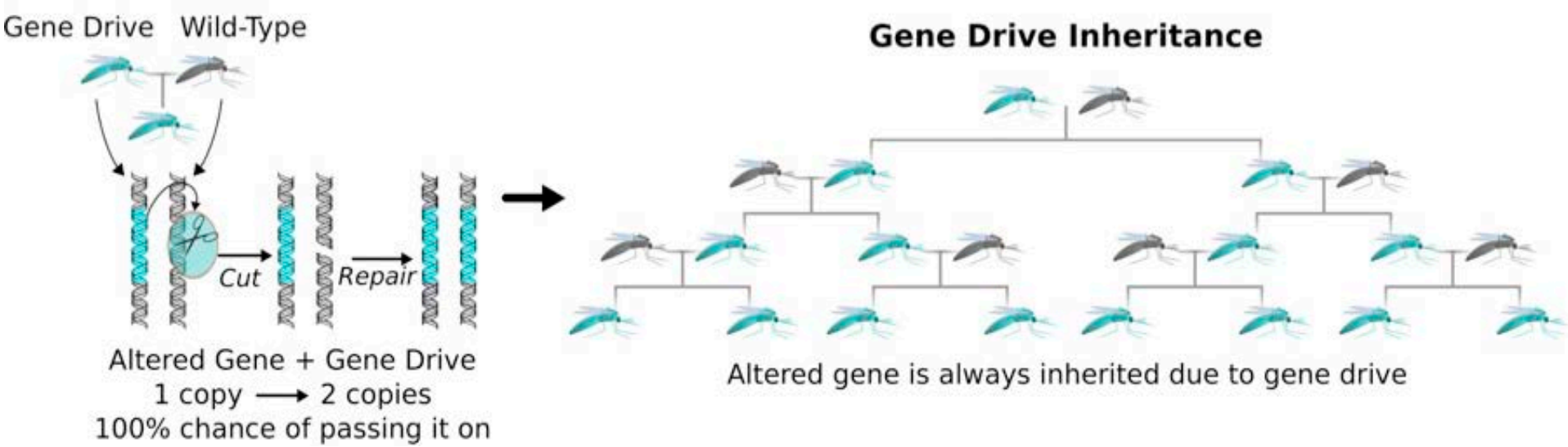
Altered gene does not increase

Gene drive


Gene Drive
Wild-Type
Cut
Repair
Altered Gene + Gene Drive
1 copy ⟶ 2 copies
100% chance of passing it on


Gene Drive Inheritance

Gene drive


Gene Drive
Wild-Type
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Altered Gene + Gene Drive
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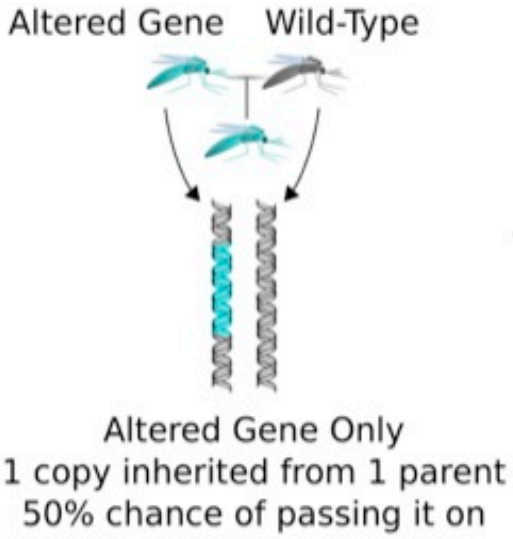
100% chance of passing it on
Gene Drive Inheritance
Altered gene is always inherited due to gene drive

Gene drive


Altered Gene
Wild-Type
Altered Gene Only
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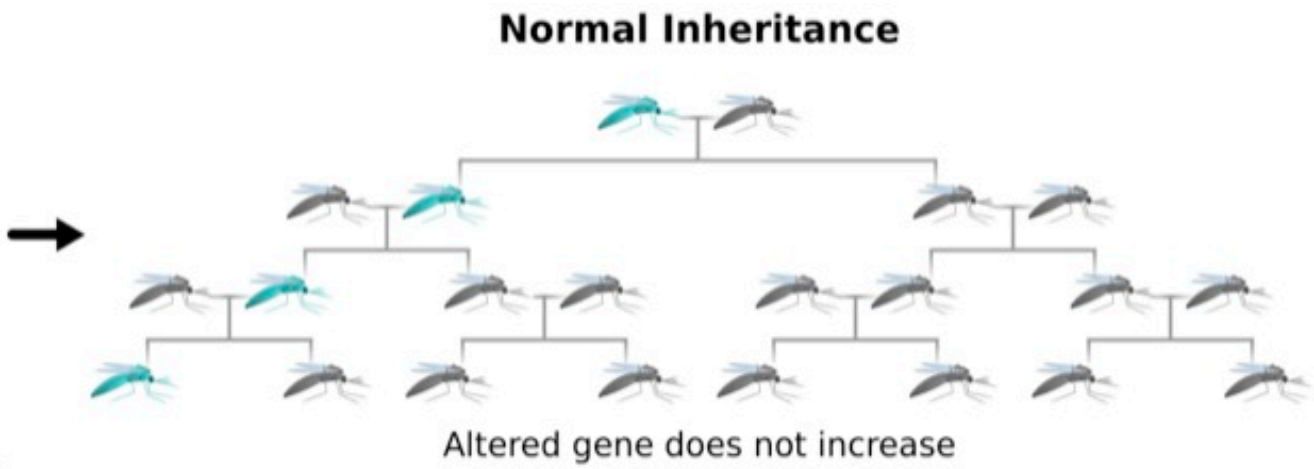
50% chance of passing it on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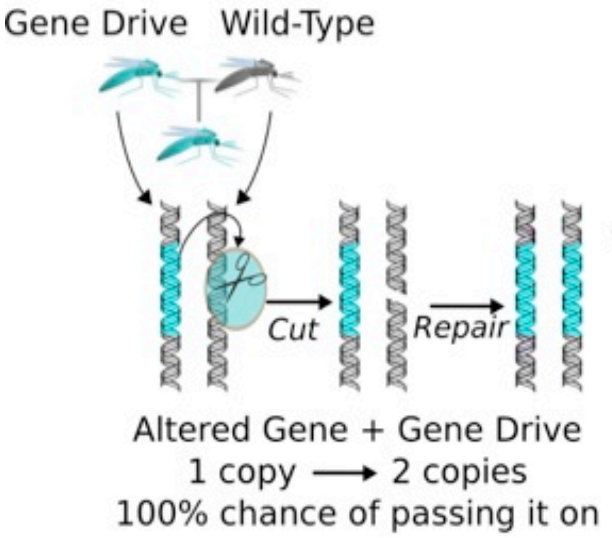
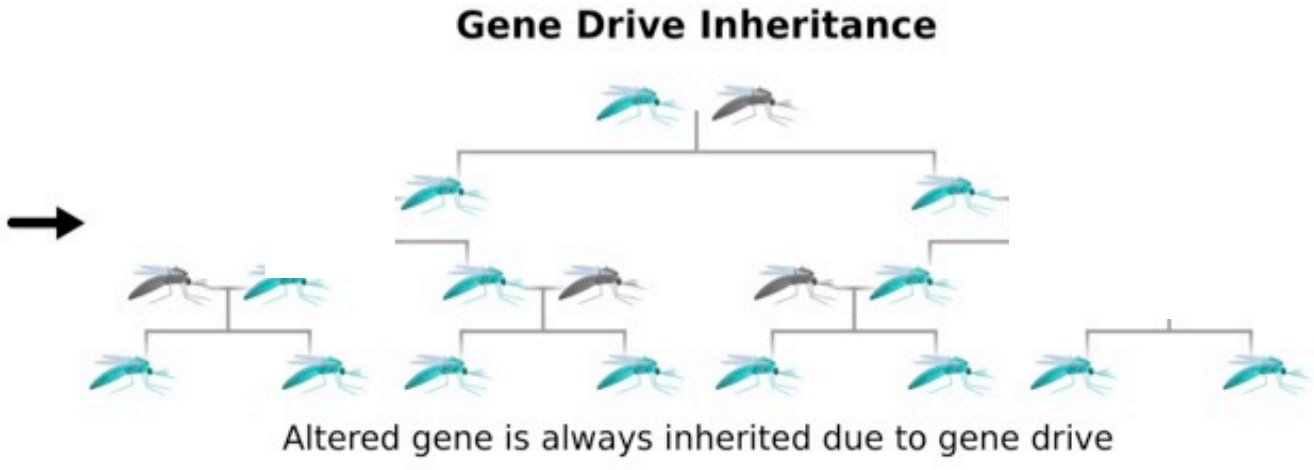
Altered gene does not increase


Gene Drive
Wild-Type
Cut
Repair
Altered Gene + Gene Drive
1 copy ⟶ 2 copies
100% chance of passing it on


Gene Drive Inheritance
Altered gene is always inherited due to gene drive

Acknowledgement

Yonsei University

- JungHa Lee, PhD
- Bharathi Ramakrishna, PhD
- Ramu Gopalappa, MS
- Myungjae Song, MS
- Young-Hoon Kim, MS
- Hui Kwon Kim, MS
- Eun-Seo Lee, MS
- JeongHong Shin
- SangEun Lee

Seoul National University

Jin-Soo Kim lab

Hanyang University

Jin-Wu Nam lab

- Suresh Ramakrishna, PhD
- Abu-bonsrah Kwaku Dad

Active collaboration

Yonsei University

-김응권 교수님
-이민구 교수님
-강훈철 교수님
-Dong-Wook Kim lab
-Sung-Rae Cho lab
-Seung-Woo Cho lab
-천진우 교수님

-…..**more than 10 labs (>70% Yonsei University)**

연세대학교 약리학교실
DEPARTMENT OF PHARMACOLOGY
YONSEI UNIVERSITY COLLEGE OF MEDICINE

Thank you!!!

If you are interested in joining our lab, please contact us.

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